Metal-Free Photochemical Imino-Alkylation of Alkenes with Bifunctional Oxime Esters

Jadab Majhi,

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

Roshan K. Dhungana[§],

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

Ángel Rentería-Gómez[§],

Department of Chemistry, Texas A&M University, College Station, Texas 77843, United States

Mohammed Sharique[§],

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

Longbo Li,

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

Weizhe Dong,

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

Osvaldo Gutierrez[*],

Department of Chemistry, Texas A&M University, College Station, Texas 77843, United States

Gary A. Molander[*]

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

GRAPHICAL ABSTRACT:

The concurrent installation of C–C and C–N bonds across alkene frameworks represents a powerful tool to prepare motifs that are ubiquitous in pharmaceuticals and bioactive compounds. To construct such prevalent bonds, most alkene difunctionalization methods demand the use of precious metals or activated alkenes. We report a metal-free, photochemically mediated imino-alkylation of electronically diverse alkenes to install both alkyl and iminyl groups in a highly efficient manner. The exceptionally mild reaction conditions, broad substrate scope, excellent

[*]**Corresponding Authors:** Osvaldo Gutierrez – *Department of Chemistry, Texas A&M University, College Station, Texas 77843, United States;* og.labs@tamu.edu; Gary A. Molander – *Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States;* gmolandr@sas.upenn.edu.
[§]Author Contributions
R.K.D., A.R.-.G., and M.S. contributed equally

functional group tolerance, and facile one-pot reaction protocol highlight the utility of this method to prepare privileged motifs from readily available alkene and acid feedstocks. One key and striking feature of this transformation is that an electrophilic trifluoromethyl radical is equally efficient with both electron-deficient and electron-rich alkenes. Additionally, dispersion-corrected density functional theory (DFT) and empirical investigations provide detailed mechanistic insight into this reaction.
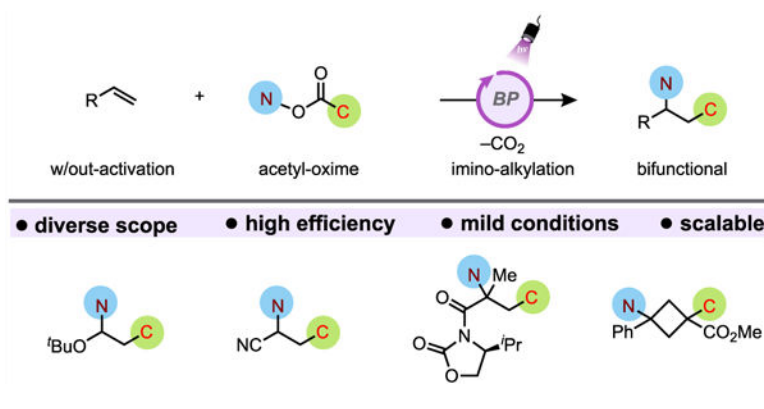
INTRODUCTION

Difunctionalization of alkenes offers a straightforward and powerful strategy for constructing structurally complex molecules, installing two chemical bonds across an alkene using readily available feedstocks. Given the most versatile and omnipresent C–C and C–N bonds in pharmaceuticals and bioactive compounds, the alkene carboamination process represents a vibrant area of investigation in organic synthesis, forging both carbon- and nitrogen-based functional units in a single operation (Figure 1a).[1–5] In this context, a wide variety of carboamination strategies have been developed such as classic arylamination,[6–10] aminocyanation,[11–13] trifluoromethylamination,[14–22] and alkylamination[23–27] to construct amines; however, these transformations are mainly limited to transition-metal-catalyzed processes. Further, despite significant progress in this arena, traditional alkene difunctionalization methods rely on the use of harsh conditions, organometallic reagents, and expensive catalysts.[1–5,28] In addition to these issues, another formidable challenge associated with this conventional manifold is the β-hydride elimination of alkylmetal intermediates, particularly for unactivated alkenes, thus limiting the use of $C(sp^3)$-hybridized alkyl groups. Despite the increasing interest in $C(sp^3)$-rich small organic molecules,[29] important areas of chemical space remain elusive within this platform. The $C(sp^3)$ bonds of fluoroalkyl groups have been of special interest because of their numerous applications in drug-discovery programs owing to the remarkable pharmacokinetic (PK) properties, hydrogen bonding capabilities, and enzymatic stability exhibited by molecules possessing C–F bonds.[30–33] Hence, the ability to incorporate both fluorinated alkyl moieties and nitrogen-based functional groups across accessible alkenes in a regioselective fashion is highly desirable.

For the construction of fluorinated alkyl- and nitrogen-based chemical bonds across an alkene, several photochemically mediated amino-trifluoromethylation strategies have been

developed to assemble the two vicinal functional groups (e.g., NR_2 and CF_3) in a single step.[15,21,34] However, the synthetic utility of these approaches is often limited because of the requirement for activated alkenes (e.g., styrene), transition-metal catalysts, and the circumscribed use of electrophilic CF_3 sources such as Togni's ($102.0/g) and Umemoto's reagents ($124.0/g). Alternatively, alkyl oxime esters provide a tactical advantage as they are capable of generating both alkyl- and nitrogen-based radicals simultaneously via a fragmentation/decarboxylation process (Figure 1b).[35–37] However, the use of oxime esters is limited because the solitary adoption of either nitrogen- or carbon-based radicals in the chemical synthesis leads to poor atom economy.[34,38–40] As a result, the use of bifunctional oxime esters in organic synthesis remains underdeveloped.

Nevertheless, fluorine and nitrogen are ubiquitous in pharmaceutical drugs: 20% of all commercialized drugs contain fluorine, including important drugs in numerous pharmaceutical classes;[41] more than 340 pharmaceuticals containing fluorine substituents have been registered over the past 65 years;[42] and presently, 75% of the FDA-approved marketed drugs are nitrogen-containing pharmaceuticals.[43,44] A straightforward and metal-free catalytic alkene difunctionalization for installation of both $C(sp^3)$-fluoroalkyl and nitrogen-based functional groups from commodity starting materials would circumvent the shortcomings of the aforementioned methods. The envisioned regio- and chemoselective metal-free catalytic photochemical vicinal imino-alkylation across unactivated alkenes with bifunctional oxime ester lynchpins (Figure 1c) would overcome the unresolved challenges and provide a powerful alternative to the conventional methods for accessing both $C(sp^3)$-fluoroalkyl and nitrogen-based functional units simultaneously across readily available feedstocks under mild and scalable conditions.

RESULTS AND DISCUSSION

In accord with the proposed hypothesis, the readily available benzophenone derivative of trifluoroacetyl oxime **1a** was selected to demonstrate proof-of-principle (Table 1). Thus, simple mixing of trifluoroacetic acid ($0.14/g) and benzophenone oxime derived from benzophenone ($0.04/g) in CH_2Cl_2 under ambient conditions yielded bifunctional trifluoroacetyl oxime **1a** (see Supporting Information (SI)). From a practical standpoint, the reaction does not require flash chromatography as the crude product can be used directly in a subsequent step without further purification or can be isolated and stored in the freezer for several months without significant decomposition. In early studies of the imino-alkylation reaction, a side reaction consisting of cross-coupling of the persistent iminyl and transient carbon radicals, affording several byproducts, posed a potential challenge.[45,46] Gratifyingly, optimization of the desired imino trifluoromethylation of unactivated 4-phenyl-1-butene with trifluoroacetyl oxime **1a** was accomplished, providing a 70% NMR yield of the desired product utilizing catalytic benzophenone (see SI). Additional studies demonstrated that the reaction functioned best in acetone solvent. Control studies confirmed the necessity of light and benzophenone catalyst for efficient reactivity, as, without benzophenone, only 30% NMR yield was observed. This was derived from the excited state oxime ester undergoing fragmentation to initiate the reaction as a result of its weak absorption in the 390 nm region of the spectrum. Ultimately, this simple method provides a convenient and practical means for constructing vicinal trifluoromethylated amine derivatives with exquisite regioselectivity.

With suitable reaction conditions in hand, the scope of imino-trifluoromethylation of trifluoroacetyl oxime with a wide variety of alkenes was evaluated (Table 1). Gratifyingly, alkenes bearing ethers, ketones, esters, amides, nitriles, and heterocycles offered minimal to no off-target reactivity, demonstrating the excellent functional group tolerance of this reaction. At the outset, we examined a range of unactivated terminal alkenes, which are unreactive under typical photoredox conditions but produced the desired products in good yield (**3–8**). In this context, ethylene gas also offers the desired product (**7**), albeit with lower efficiency. The most remarkable feature of this transformation is that an electrophilic trifluoromethyl radical is equally efficient with both electron-deficient and electron-rich alkenes presumably because of the faster kinetics associated with the pyramidal nature of this radical (**9–14**; see SI).[47–49] All the examined alkenes are well-tolerated regardless of their substitution or electronic properties.

Next, we explored a wide range of styrene derivatives with different electron-donating and electron-withdrawing groups at various positions about the aromatic ring, all of which readily underwent imino-trifluoromethylation in good yield and with excellent regioselectivity (**15–21**). Moreover, the reaction is applicable to styrene systems incorporating boronate and polyfluoro substituents, as well as heteroaromatic and polyaromatic (**22–26**) substructures. Furthermore, a range of internal alkenes also underwent imino trifluoromethylation in good yield with excellent regio- and occasionally good diastereoselectivity (**27–34**). The reaction was also performed in one pot with a minimal decrease in yield (**10, 16, 18**). These results highlight the potential application of the current process in synthetic chemistry, avoiding the requirement of workup and isolation steps for the oxime esters. Notably, the reaction was applied to several cyclic alkenes with high diastereoselectivity. The reaction also tolerates 1,1-disubstituted alkenes to yield tertiary alkylamine derivatives. Compound **34**, derived from oxazolidinone, was functionalized to generate different synthetically useful functional groups for applications in target-directed synthesis. Diethyl diallyl malonate (**35**) provides the radical cascade cyclization product **36** with good yield and excellent diastereoselectivity. Overall, the metal-free iminotrifluoromethylation reaction of trifluoroacetyl oxime (**1a**) has a broad alkene scope and provides a straightforward approach to vicinal trifluoromethylated amine compounds.

To demonstrate the general and broad application of this method for imino-alkylation, we expanded the scope of bifunctional oxime esters. Under the optimized conditions, a set of fluoro- and chloroalkyl-substituted oxime esters underwent imino-alkylation with acrylonitrile (Table 2). Several oxime esters of chloroacetic acids, such as mono-, di-, and trichloroacetyl oxime esters, proved to be effective substrates (**37–39**). Notably, a range of fluoro-substituted oxime esters were tolerated (**40–42**). This is a significant development, given that all these electrophilic radicals react equally well with an electrophilic alkene. Next, our attention turned to an investigation of the scope of alkyl acid derivatives. Methyl, bicyclo[1.1.1]pentyl (BCP), and cubyl groups have attracted recent attention in drug discovery owing to the dramatic change in affinity and enhanced pharmacokinetic properties, including improvement of aqueous solubility and membrane permeability.[50–52] Encouraged by the several pivotal roles of these motifs, we explored the feasibility of

incorporating these substructures in the current iminoalkylation protocol. Gratifyingly, methyl-, BCP-, and cubyl oxime-esters provided the desired alkylated products (**43–45**) in good yields and with excellent regioselectivities. To highlight the potential utility of the current methods, a gram-scale reaction furnished the desired product (**11**) with commensurable levels of efficiency without the use of any specialized glassware, equipment, or irradiation source. Perhaps most strikingly, a [1.1.0]-bicyclobutane derivative provides the desired product (**46**) in reasonable yield. This process highlights the utility of imino-alkylation reaction to prepare challenging small- and strained ring scaffolds that are prevalent in bioactive molecules that display improved pharmacokinetic properties.[53–56]

The expedited generation of molecular complexity from readily available starting materials is a preeminent goal in synthetic chemistry. The treatment of acetyl oxime ester with electron-rich and electron-poor alkenes generated a multi-component cascade product (**47**) in good yield.[57] This simple protocol provides an exemplary showcase of radical polarity matching that installs several functional groups (e.g., CF_3, ether, nitrile, and imine) by making three new bonds in a single operation from convenient feedstocks. Finally, a mild deprotection step[58] affords the corresponding β-CF_3 amine (**48**) and recovery of benzophenone with excellent yield.

To gain insights into the mechanism and origin of reactivity and regioselectivity, we turned to dispersion-corrected density functional theory (DFT) calculations (see the SI for additional details). As shown in Figure 2, energy transfer between the photocatalyst and the oxime $\mathbf{A^1}$ leads to rapid fragmentation/decarboxylation (N–O bond cleavage in the triplet state $\mathbf{A^3}$ takes place through a small energy barrier, $\Delta G^{\ddagger} = 1.0$ kcal/mol) of the excited oxime ester $\mathbf{A^3}$ (49.7 kcal/mol uphill in energy, which is sufficient to undergo triplet–triplet energy transfer with an excited benzophenone) to generate the $CF_3{}^{\bullet}$ radical and N-centered diphenyliminyl radical pair with concomitant release of CO_2 (36.2 kcal/mol downhill in energy from excited state intermediate $\mathbf{A^3}$).[46] Given that both electron-deficient and electron-rich alkenes were equally effective in this transformation, we considered both π-components in these calculations. Notably, we hypothesized that the long lifetime of the diphenyliminyl radical $\mathbf{C}$[36] should allow the transient $CF_3{}^{\bullet}$ to escape the solvent cage and add, regioselectively, to the terminal position of the alkene to generate the more-stabilized radical $\mathbf{II}$. DFT calculations revealed that the radical addition of $CF_3{}^{\bullet}$ onto acrylonitrile or *tert*-butyl vinyl ether $\mathbf{I}$ (via $\mathbf{TS1}$) proceeds irreversibly via a low energy barrier (7.3 and 6.7 kcal/mol, respectively) to deliver the intermediate $\mathbf{II}$, downhill in energy by 27–32 kcal/mol. In addition, we also considered an alternative pathway in which the diphenyliminyl radical $\mathbf{C}$ adds to the alkene via $\mathbf{TS1'}$ but, consistent with experiment, the energy barrier was considerably higher compared to $\mathbf{TS1}$ (~10 kcal/mol). Alternative radical addition pathways (via $\mathbf{TS'}$, $\mathbf{TS''}$, and $\mathbf{TS'''}$) were found to be much higher in energy and thus were not considered further.

Next, selective radical–radical cross-coupling between $\mathbf{II}$ and $\mathbf{C}$ would be kinetically feasible based on the persistent radical effect (PRE)[3] and has been previously proposed as the major mechanistic pathway.[36] However, because a radical–radical cross-coupling approach possesses numerous challenges connected to potentially unproductive pathways outcompeting the desired reaction,[59,60] we propose an alternative mechanistic pathway that

accounts for the high efficiency and selectivity. We envisioned intermediate **II** engaging as a radical chain mediator, in which it can engage with another molecule of oxime ester. Given that the relative concentration of oxime ester is much higher than iminyl radical **C**, in this mechanistic pathway, **II** undergoes selective addition onto oxime ester (^{1}**A**)[61,62] through **TS2** with an energy barrier of 19.9 kcal/mol (R = −CN) and 10.4 kcal/mol (R = −O′Bu) with respect to **II**,[63] leading to intermediate **III** which, in turn, quickly undergoes fragmentation to form the desired product **IV** and concomitant release of CF_3CO_2·. Finally, after facile decarboxylation to form CO_2 and the CF_3 radical ($G^{\ddagger} = $ 1.0 kcal/mol), the CF_3 radical can, in turn, add selectively to another alkene to restart the cycle. Consistent with this scenario, the measured quantum yield for the reaction (**Φ**) is 2.4, an experimental measure that is in line with a mechanism transpiring through a chain process but not one proceeding via the persistent radical effect alone.

Notably, both energy barriers are feasible under the reaction conditions and consistent with experiments (Table 2) where calculations predict faster ·CF_3 radical addition to electron-rich alkenes. In addition, we also considered an alternative path for the addition of the radical **II** onto the oxime ester (^{1}**A**) through **TS2′** but ruled out this pathway based on a higher energy barrier compared to **TS2**.[63]

CONCLUSONS

In conclusion, the method described herein provides a metal-free, photochemically mediated imino-alkylation of electronically diverse alkenes to install both carbon and nitrogen units in a highly atom-economical fashion. The developed protocol offers mild reaction conditions, broad substrate scope, excellent functional group tolerance, and facile gram-scale as well as one-pot reaction manipulation, highlighting the utility of this protocol to prepare privileged motifs from readily available alkene and acid feedstocks. The new reagent is a potential source of two important functional groups: CF_3 and iminyl motifs. The developed method is applicable to a cascade-type reaction to generate molecular complexity from readily available starting materials. In addition, computer simulations and experimental investigations provide previously unrecognized mechanistic insight into the observed reactivity of this reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

REFERENCES

(1). Chemler SR; Fuller PH Heterocycle synthesis by copper facilitated addition of heteroatoms to alkenes, alkynes and arenes. Chem. Soc. Rev 2007, 36, 1153–1160. [PubMed: 17576482]

(2). Müller TE; Hultzsch KC; Yus M; Foubelo F; Tada M Hydroamination: Direct Addition of Amines to Alkenes and Alkynes. Chem. Rev 2008, 108, 3795–3892. [PubMed: 18729420]

(3). Jiang H; Studer A Intermolecular radical carboamination of alkenes. Chem. Soc. Rev 2020, 49, 1790–1811. [PubMed: 32055811]

(4). Chen X; Xiao F; He W-M Recent developments in the difunctionalization of alkenes with C–N bond formation. Org. Chem. Front 2021, 8, 5206–5228.

(5). Hirano K; Miura M Hydroamination, Aminoboration, and Carboamination with Electrophilic Amination Reagents: Umpolung-Enabled Regio- and Stereoselective Synthesis of N-Containing Molecules from Alkenes and Alkynes. J. Am. Chem. Soc 2022, 144, 648–661. [PubMed: 34986637]

(6). Bao H; Bayeh L; Tambar UK Regioselective and diastereoselective aminoarylation of 1,3-dienes. Chem. Sci 2014, 5, 4863–4867. [PubMed: 25431651]

(7). Fumagalli G; Boyd S; Greaney MF Oxyarylation and Aminoarylation of Styrenes Using Photoredox Catalysis. Org. Lett 2013, 15, 4398–4401. [PubMed: 23927030]

(8). Lerchen A; Knecht T; Daniliuc CG; Glorius F Unnatural Amino Acid Synthesis Enabled by the Regioselective Cobalt(III)-Catalyzed Intermolecular Carboamination of Alkenes. Angew. Chem., Int. Ed 2016, 55, 15166–15170.

(9). Prasad Hari D; Hering T; König B The Photoredox-Catalyzed Meerwein Addition Reaction: Intermolecular Amino-Arylation of Alkenes. Angew. Chem., Int. Ed 2014, 53, 725–728.

(10). Liu Z; Wang Y; Wang Z; Zeng T; Liu P; Engle KM Catalytic Intermolecular Carboamination of Unactivated Alkenes via Directed Aminopalladation. J. Am. Chem. Soc 2017, 139, 11261–11270. [PubMed: 28727452]

(11). Kwon Y; Wang Q Copper-Catalyzed 1,2-Aminocyanation of Unactivated Alkenes via Cyano Migration. Org. Lett 2020, 22, 4141–4145. [PubMed: 32383382]

(12). Xu L; Mou X-Q; Chen Z-M; Wang S-H Coppercatalyzed intermolecular azidocyanation of aryl alkenes. Chem. Commun 2014, 50, 10676–10679.

(13). Zhang H; Pu W; Xiong T; Li Y; Zhou X; Sun K; Liu Q; Zhang Q Copper-Catalyzed Intermolecular Aminocyanation and Diamination of Alkenes. Angew. Chem., Int. Ed 2013, 52, 2529–2533.

(14). Carboni A; Dagousset G; Magnier E; Masson G Photoredox-Induced Three-Component Oxy-, Amino-, and Carbotrifluoromethylation of Enecarbamates. Org. Lett 2014, 16, 1240–1243. [PubMed: 24520865]

(15). Dagousset G; Carboni A; Magnier E; Masson G Photoredox-Induced Three-Component Azido- and Aminotrifluoromethylation of Alkenes. Org. Lett 2014, 16, 4340–4343. [PubMed: 25102254]

(16). Kawamura S; Egami H; Sodeoka M Aminotrifluoromethylation of Olefins via Cyclic Amine Formation: Mechanistic Study and Application to Synthesis of Trifluoromethylated Pyrrolidines. J. Am. Chem. Soc 2015, 137, 4865–4873. [PubMed: 25798656]

(17). Lin J-S; Dong X-Y; Li T-T; Jiang N-C; Tan B; Liu X-Y A Dual-Catalytic Strategy To Direct Asymmetric Radical Aminotrifluoromethylation of Alkenes. J. Am. Chem. Soc 2016, 138, 9357–9360. [PubMed: 27414501]

(18). Shen K; Wang Q Copper-catalyzed aminotrifluoromethylation of alkenes: a facile synthesis of CF_3-containing lactams. Org. Chem. Front 2016, 3, 222–226.

(19). Wang F; Qi X; Liang Z; Chen P; Liu G Copper-Catalyzed Intermolecular Trifluoromethylazidation of Alkenes: Convenient Access to CF3-Containing Alkyl Azides. Angew. Chem., Int. Ed. 2014, 53, 1881–1886.

(20). Xiao H; Shen H; Zhu L; Li C Copper-Catalyzed Radical Aminotrifluoromethylation of Alkenes. J. Am. Chem. Soc 2019, 141, 11440–11445. [PubMed: 31283210]

(21). Yasu Y; Koike T; Akita M Intermolecular Aminotrifluoromethylation of Alkenes by Visible-Light-Driven Photoredox Catalysis. Org. Lett 2013, 15, 2136–2139. [PubMed: 23600821]

(22). Zhu C-L; Wang C; Qin Q-X; Yruegas S; Martin CD; Xu H Iron(II)-Catalyzed Azidotrifluoromethylation of Olefins and N-Heterocycles for Expedient Vicinal Trifluoromethyl Amine Synthesis. ACS Catal 2018, 8, 5032–5037. [PubMed: 29938121]

(23). Liu Y-Y; Yang X-H; Song R-J; Luo S; Li J-H Oxidative 1,2-carboamination of alkenes with alkyl nitriles and amines toward γ-amino alkyl nitriles. Nat. Commun 2017, 8, 14720. [PubMed: 28393864]

(24). Qian B; Chen S; Wang T; Zhang X; Bao H Iron-Catalyzed Carboamination of Olefins: Synthesis of Amines and Disubstituted β-Amino Acids. J. Am. Chem. Soc 2017, 139, 13076–13082. [PubMed: 28857555]

(25). Zhang Y; Liu H; Tang L; Tang H-J; Wang L; Zhu C; Feng C Intermolecular Carboamination of Unactivated Alkenes. J. Am. Chem. Soc 2018, 140, 10695–10699. [PubMed: 30102522]

(26). Piou T; Rovis T Rhodium-catalysed syn-carboamination of alkenes via a transient directing group. Nature 2015, 527, 86–90. [PubMed: 26503048]

(27). Lu D; Li Y; Wang P; Wang Z; Yang D; Gong Y Cu-Catalyzed C(sp3)–N Coupling and Alkene Carboamination Enabled by Ligand-Promoted Selective Hydrazine Transfer to Alkyl Radicals. ACS Catal 2022, 12, 3269–3278.

(28). McDonald RI; Liu G; Stahl SS Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications. Chem. Rev 2011, 111, 2981–3019. [PubMed: 21428440]

(29). Lovering F; Bikker J; Humblet C Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. J. Med. Chem 2009, 52, 6752–6756. [PubMed: 19827778]

(30). Böhm H-J; Banner D; Bendels S; Kansy M; Kuhn B; Muller K; Obst-Sander U; Stahl M Fluorine in Medicinal Chemistry. ChemBioChem 2004, 5, 637–643. [PubMed: 15122635]

(31). Gillis EP; Eastman KJ; Hill MD; Donnelly DJ; Meanwell NA Applications of Fluorine in Medicinal Chemistry. J. Med. Chem 2015, 58, 8315–8359. [PubMed: 26200936]

(32). Meanwell NA Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. J. Med. Chem 2018, 61, 5822–5880. [PubMed: 29400967]

(33). Müller K; Faeh C; Diederich F Fluorine in Pharmaceuticals: Looking Beyond Intuition. Science 2007, 317, 1881–1886. [PubMed: 17901324]

(34). Geng X; Lin F; Wang X; Jiao N Azidofluoroalkylation of Alkenes with Simple Fluoroalkyl Iodides Enabled by Photoredox Catalysis. Org. Lett 2017, 19, 4738–4741. [PubMed: 28876952]

(35). Rykaczewski KA; Wearing ER; Blackmun DE; Schindler CS Reactivity of oximes for diverse methodologies and synthetic applications. Nat. Synth 2022, 1, 24–36.

(36). Patra T; Bellotti P; Strieth-Kalthoff F; Glorius F Photosensitized Intermolecular Carboimination of Alkenes through the Persistent Radical Effect. Angew. Chem., Int. Ed 2020, 59, 3172–3177.

(37). Xia P-J; Liu F; Pan Y-M; Yang M-P; Yang Y-Y Efficient access to β-amino acid ester/β-amino ketone derivatives via photocatalytic radical alkoXycabonylimidation/carbonylimidation of alkenes. Org. Chem. Front 2022, 9, 2522–2528.

(38). Patra T; Mukherjee S; Ma J; Strieth-Kalthoff F; Glorius F Visible-Light-Photosensitized Aryl and Alkyl Decarboxylative Functionalization Reactions. Angew. Chem., Int. Ed 2019, 58, 10514–10520.

(39). Davies J; Sheikh NS; Leonori D Photoredox Imino Functionalizations of Olefins. Angew. Chem., Int. Ed 2017, 56, 13361–13365.

(40). Cai S-H; Xie J-H; Song S; Ye L; Feng C; Loh T-P Visible-Light-Promoted Carboimination of Unactivated Alkenes for the Synthesis of Densely Functionalized Pyrroline Derivatives. ACS Catal 2016, 6, 5571–5574.

(41). Emsley J Nature's building blocks: An A–Z. guide to the elements, 2nd ed.; Oxford University Press: 2011; p 178.

(42). Inoue M; Sumii Y; Shibata N Contribution of Organofluorine Compounds to Pharmaceuticals. ACS Omega 2020, 5, 10633–10640. [PubMed: 32455181]

(43). Heravi MM; Zadsirjan V Prescribed drugs containing nitrogen heterocycles: an overview. RSC Adv 2020, 10, 44247–44311. [PubMed: 35557843]

(44). Kerru N; Gummidi L; Maddila S; Gangu KK; Jonnalagadda SB A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. Molecules 2020, 25, 1909. [PubMed: 32326131]

(45). Hasebe M; Kogawa K; Tsuchiya T Photochemical arylation by oxime esters in benzene and pyridine: simple synthesis of biaryl compounds. Tetrahedron Lett 1984, 25, 3887–3890.

(46). Soni VK; Lee S; Kang J; Moon YK; Hwang HS; You Y; Cho EJ Reactivity Tuning for Radical–Radical Cross-Coupling via Selective Photocatalytic Energy Transfer: Access to Amine Building Blocks. ACS Catal 2019, 9, 10454–10463.

(47). Pan X; Xia H; Wu J Recent advances in photoinduced trifluoromethylation and difluoroalkylation. Org. Chem. Front 2016, 3, 1163–1185.

(48). Tang X-J; Zhang Z; Dolbier WR Jr. Direct Photoredox-Catalyzed Reductive Difluoromethylation of Electron-Deficient Alkenes. Chem.—Eur. J 2015, 21, 18961–18965. [PubMed: 26527168]

(49). Yoshioka E; Kohtani S; Sawai K; Kentefu; Tanaka E; Miyabe H Polarity-Mismatched Addition of Electrophilic Carbon Radicals to an Electron-Deficient Acceptor: Cascade Radical Addition–Cyclization–Trapping Reaction. J. Org. Chem 2012, 77, 8588–8604. [PubMed: 22963515]

(50). Aynetdinova D; Callens MC; Hicks HB; Poh CYX; Shennan BDA; Boyd AM; Lim ZH; Leitch JA; Dixon DJ Installing the "magic methyl" – C–H methylation in synthesis. Chem. Soc. Rev 2021, 50, 5517–5563. [PubMed: 33690769]

(51). Bauer MR; Di Fruscia P; Lucas SCC; Michaelides IN; Nelson JE; Storer RI; Whitehurst BC Put a ring on it: application of small aliphatic rings in medicinal chemistry. RSC Med. Chem 2021, 12, 448–471. [PubMed: 33937776]

(52). Reekie TA; Williams CM; Rendina LM; Kassiou M Cubanes in Medicinal Chemistry. J. Med. Chem 2019, 62, 1078–1095. [PubMed: 30137982]

(53). Carreira EM; Fessard TC Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. Chem. Rev 2014, 114, 8257–8322. [PubMed: 25003801]

(54). Dembitsky VM Naturally occurring bioactive Cyclobutane-containing (CBC) alkaloids in fungi, fungal endophytes, and plants. Phytomedicine 2014, 21, 1559–1581. [PubMed: 25442265]

(55). Li J; Gao K; Bian M; Ding H Recent advances in the total synthesis of cyclobutane-containing natural products. Org. Chem. Front 2020, 7, 136–154.

(56). van der Kolk MR; Janssen MACH; Rutjes FPJT; Blanco-Ania D Cyclobutanes in Small-Molecule Drug Candidates. ChemMedChem 2022, 17, e202200020. [PubMed: 35263505]

(57). Tu H-Y; Zhu S; Qing F-L; Chu L A four-component radical cascade trifluoromethylation reaction of alkenes enabled by an electron-donor–acceptor complex. Chem. Commun 2018, 54, 12710–12713.

(58). Górski B; Barthelemy A-L; Douglas JJ; Juliá F; Leonori D Copper-catalysed amination of alkyl iodides enabled by halogen-atom transfer. Nat. Catal 2021, 4, 623–630.

(59). Fischer H The Persistent Radical Effect: A Principle for Selective Radical Reactions and Living Radical Polymerizations. Chem. Rev 2001, 101, 3581–3610. [PubMed: 11740916]

(60). Leifert D; Studer A The Persistent Radical Effect in Organic Synthesis. Angew. Chem., Int. Ed 2020, 59, 74–108.

(61). Viswanathan R; Mutnick D; Johnston JN The First Azacyclopentenyl Carbinyl Radical Isomerizations (ACCRI): Independent Use of Steric and Electronic (Polarization) Effects as Gating Elements. J. Am. Chem. Soc 2003, 125, 7266–7271. [PubMed: 12797800]

(62). Wei D; Liu T; He Y; Wei B; Pan J; Zhang J; Jiao N; Han B Radical 1,4/5-Amino Shift Enables Access to Fluoroalkyl-Containing Primary β(γ)-Aminoketones under Metal-Free Conditions. Angew. Chem., Int. Ed 2021, 60, 26308–26313.

(63). Schiesser CH; Wille U; Matsubara H; Ryu I Radicals Masquerading as Electrophiles: Dual Orbital Effects in Nitrogen-Philic Acyl Radical Cyclization and Related Addition Reactions. Acc. Chem. Res 2007, 40, 303–313. [PubMed: 17444607]
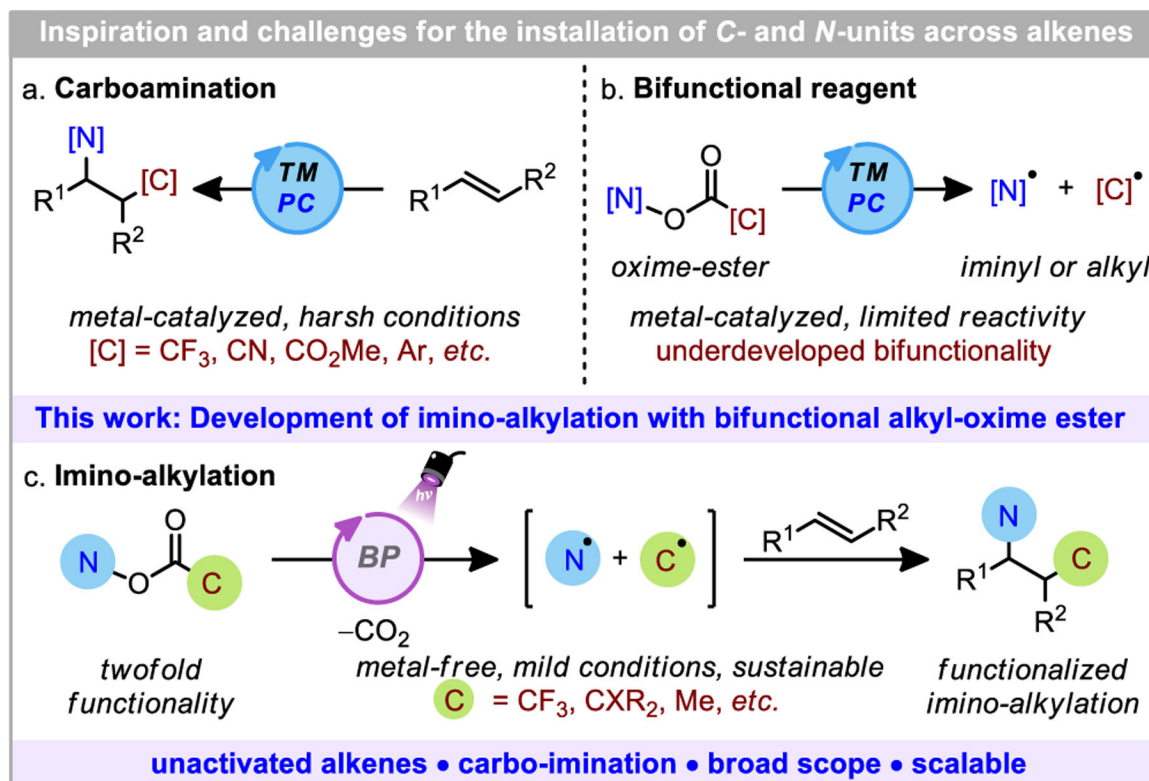
Figure 1. Background for the development of imino-alkylation of alkenes with bifunctional esters (TM = transition metal, PC = photocatalyst, BP = benzophenone).
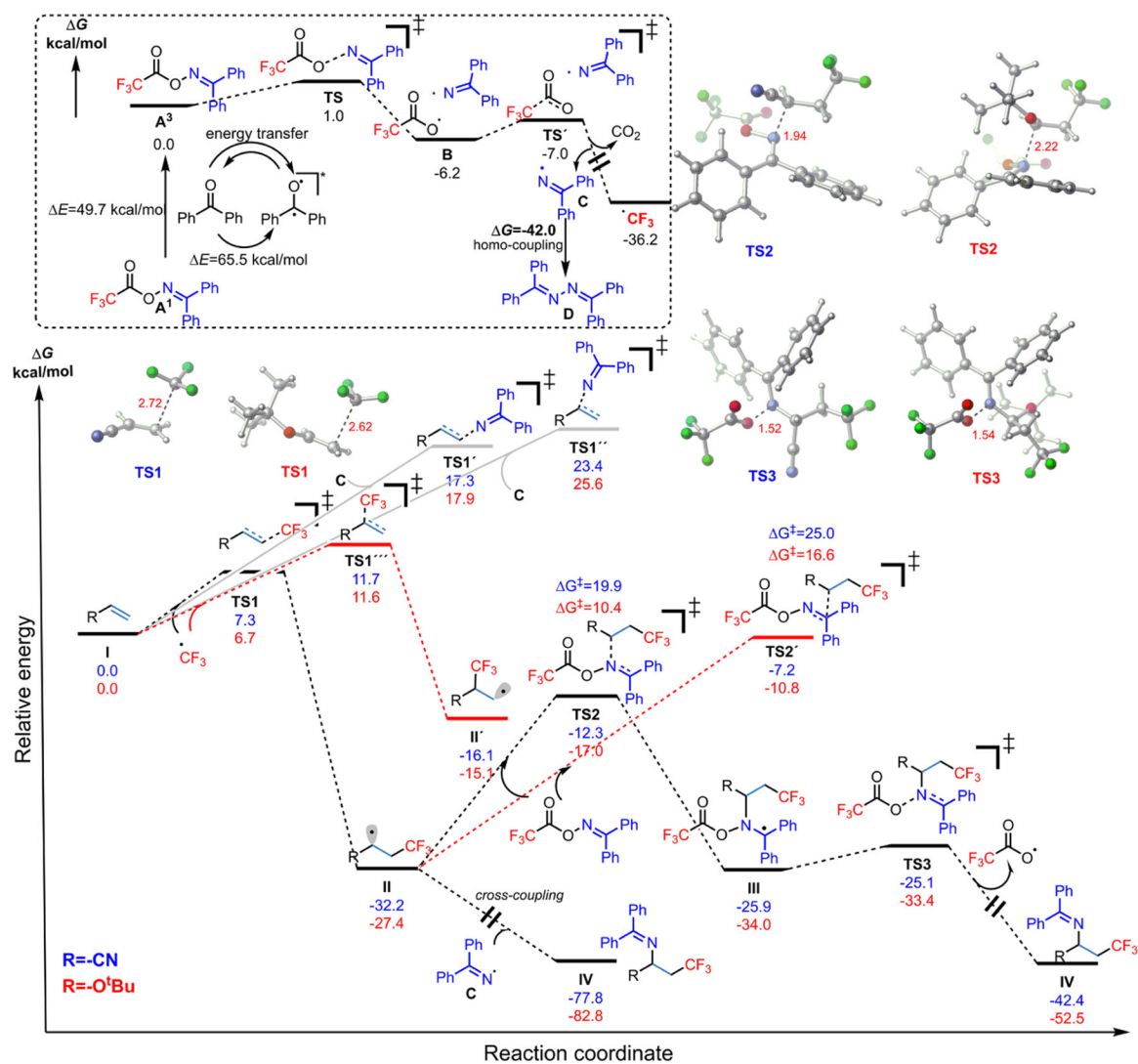
Figure 2. Proposed mechanism supported by computational studies. Calculated free Gibbs energies [CPCM(acetone) uB3LYP-d3/def2-svp] are given in kcal mol^{-1}. For details see the Supporting Information.

Table 1.

Scope of Alkenes in the Imino-Trifluoromethylation of Trifluoroacetyl Oxime[a]

Table 2.

Scope of Bifunctional Oxime Esters in the Imino-Alkylation with Acrylonitrile[a]
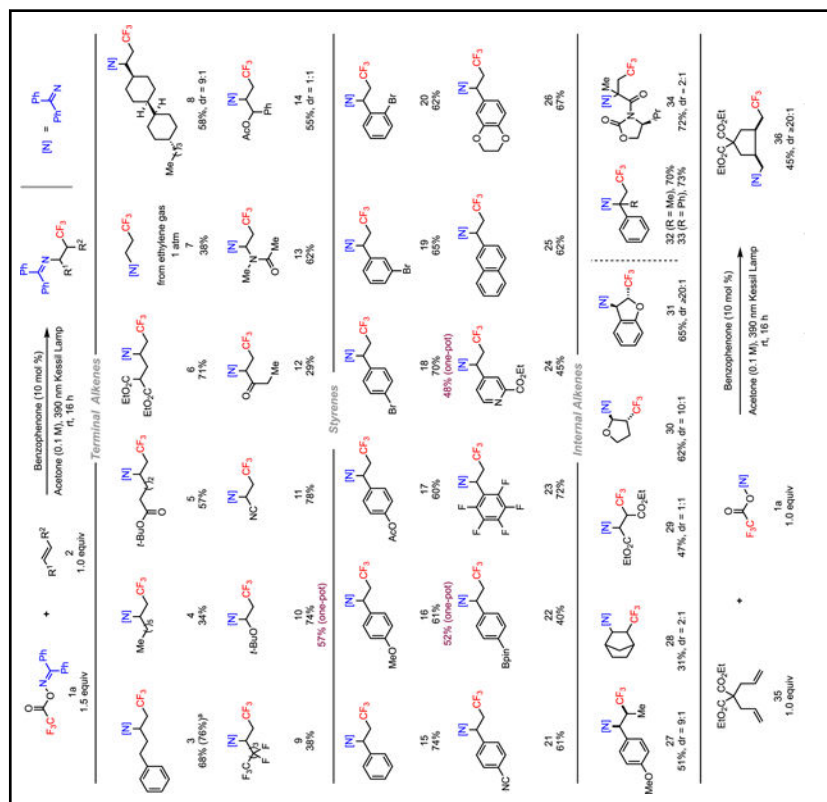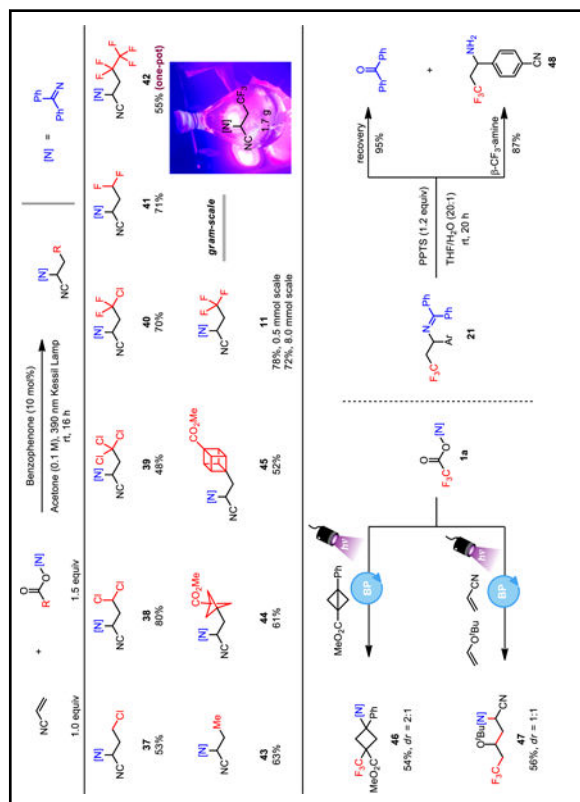
[a] All values indicate the yield of the isolated product. Unless otherwise noted: alkene (1 equiv, 0.5 mmol), trifluoroacetyl oxime (1.5 equiv, 0.75 mmol), benzophenone (10 mol %, 0.05 mmol), acetone (0.1 M), 16 h, irradiating with a 390 nm PR160 Kessil lamp.