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Direct catalytic photodecarboxylative amination of carboxylic acids with diazirines for divergent access to nitrogen-containing compounds

Vishala Maharaj[1], **Paresh R. Athawale**[2], **Preeti P. Chandrachud**[2], **Justin M. Lopchuk**[1,2,3,4,*]

[1]Department of Chemistry, University of South Florida, Tampa, FL 33620, USA

[2]Drug Discovery Department, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, FL 33612, USA

[3]Department of Oncologic Sciences, College of Medicine, University of South Florida, Tampa, FL 33612, USA

[4]Lead contact

SUMMARY

Amines, hydrazines, and nitrogen-containing heterocycles are pivotal species in medicine, agriculture, fine chemicals, and materials. Diazirines have been recently reported to serve as versatile electrophilic amination reagents for the synthesis of building blocks or late-stage C–N bond formation. Here, we report the catalytic photodecarboxylative amination of carboxylic acids with diazirines under mild conditions. The substrate scope includes broad functional group tolerance, such as ketones, esters, olefins, and alcohols, along with the late-stage amination of naproxen, ibuprofen, gemfibrozil, and gibberellic acid. Synthetic applications leverage the versatility of the intermediate diaziridines and include the regioselective preparation of a suite of 1*H*-indazoles, 2*H*-indazoles, and fluoroquinolones.

Graphical Abstract

*Correspondence: justin.lopchuk@moffitt.org.

AUTHOR CONTRIBUTIONS

V.M., P.P.C., and J.M.L. conceived and designed the project. V.M., P.R.A., and P.P.C. performed the experimental studies. V.M., P.R.A., P.P.C., and J.M.L. analyzed and interpreted experimental data. V.M., P.R.A., and J.M.L. wrote the manuscript.

SUPPLEMENTAL INFORMATION

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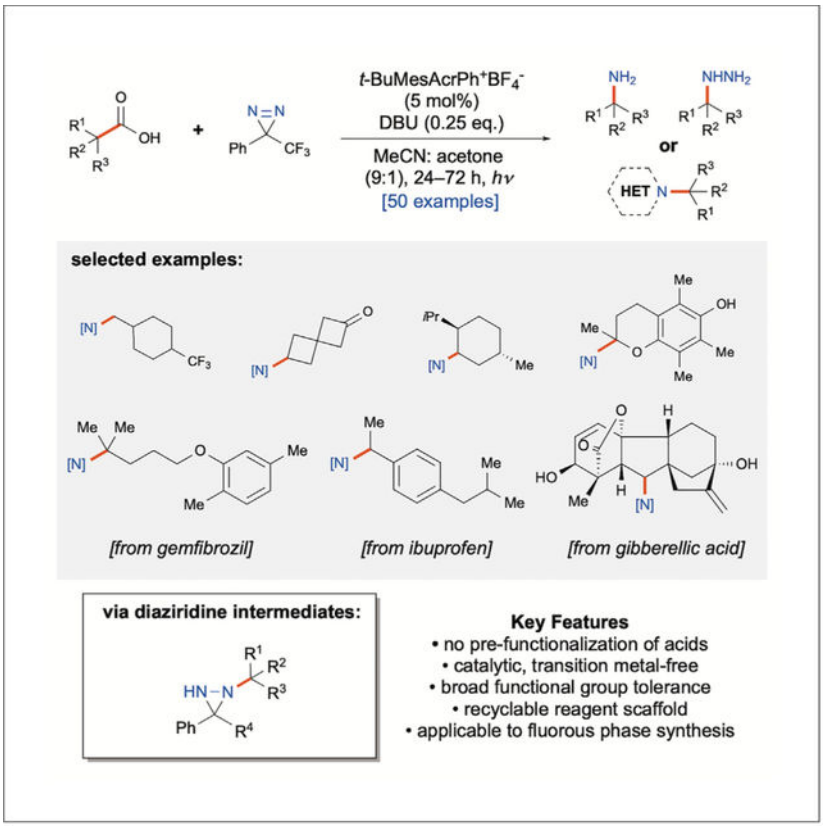
DECLARATION OF INTERESTS

The authors declare no competing interests.



Maharaj et al. report an acridinium-catalyzed photodecarboxylative amination using diazirines as an electrophilic amination reagent, demonstrated across 50 examples. The protocol allows for the rapid synthesis of aliphatic amines and hydrazines, with further diversification to a variety of nitrogen-containing heterocycles.

INTRODUCTION

The concise preparation of nitrogen-containing building blocks and the late-stage incorporation of nitrogen onto complex scaffolds are of critical importance across a variety of fields including medicine, agriculture, fine chemicals, and materials.[1–5] Consequently, the development of new chemical tools to forge C–N bonds from readily available starting materials with high chemo- and regioselectivity remains a high priority among organic chemists. Moreover, the development of pharmaceutically relevant compounds, such as those shown in Figure 1A, heavily relies on a facile diversification of the corresponding heterocycles, which is inexorably tied to the ease and versatility with which the C–N bonds can be crafted. Traditional routes to substituted alkyl amines and hydrazines involve either nucleophilic substitution with alkyl halides (often limited to 1° and 2° alkyl halides) or reductive amination.[6–11] The alkylation of nitrogen-containing heterocycles tends to employ harsh conditions and is often plagued by regioselectivity problems.

The classic conversion of carboxylate derivatives to amines through Curtius- or Hofmann-type rearrangements has been largely superseded by modern decarboxylative[12–19] amination

approaches, which can often progress under mild conditions with good functional group tolerance through the use of carboxylic acids and their derivatives, such as ‘‘redox-active’’ esters (RAEs), as the alkyl component in place of alkyl halides, ketones, or aldehydes.[20–26] This is due in part to the structural diversity, stability, and abundant commercial availability of carboxylic acids, coupled with the ease of synthesis and activation of RAEs. Previously, we demonstrated two methods for the decarboxylative amination of RAEs with diazirines as the nitrogen source.[27,28] The intermediate diaziridines were shown to serve as masked amines and hydrazines that could be further used to make a variety of heterocycles in one-pot and telescoped protocols. The stability of diazirines under blue light irradiation was also demonstrated, in contrast to expectations given their archetypical use as photoaffinity labeling groups (Figure 1B).[28,29] The use of RAEs still has several limitations, however: some carboxylic acid precursors show poor reactivity to RAE activation, RAEs can show instability during purification and handling or decompose during activation, and their preparation takes an extra synthetic step.[30] This prompted us to search for a way to engage the carboxylic acids directly with diazirines.

Acridinium-based catalysts have been developed to overcome the sustainability issues with low abundance Irand Ru-based catalysts.[31–36] These acridinium catalysts provide a stable system for alkyl radical generation from carboxylic acids and can be used to add to various radical acceptors. Despite the ability of the acridinium catalysts to generate alkyl radicals under mild, visible light conditions, their use for C–N bond-forming reactions remains underexplored. In 2016, Tunge reported the decarboxylative amination of carboxylic acids in the presence of an acridinium photocatalyst with blue light-emitting diodes (LEDs) and diisopropyl azodicarboxylate as the nitrogen source.[37] Inspired by the combination of this report and our own data regarding the evident stability of diazirines under blue light irradiation, we developed a catalytic, diversifiable photodecarboxylative amination of carboxylic acids. Here, we report fifty examples of primary, secondary, and tertiary carboxylic acids with a functional group tolerance that includes ketones, esters, olefins, alcohols, and carbamates, along with perfluorinated examples that allow for an entry into fluorous phase chemistry (Figure 1C). The growing toolkit of heterocyclic syntheses is reported with regioselective preparations of 1*H*-indazoles, 2*H*-indazoles, and the 4-quinolone core of fluoroquinolone antibiotics. This method combines the catalytic features of our original report with the broad scope and mild conditions of the second-generation approach to provide a streamlined way to directly convert feedstock carboxylic acids into high-value nitrogen-containing compounds.

RESULTS AND DISCUSSION

Reaction development and optimization

The investigation commenced with 1-tosyl-4-piperidinic acid **1** as the model sub-strate (Figure 2). The acid (1 equiv) was treated with diazirine **2** (1.25 equiv) in the presence of the organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.25 equiv) and catalytic 9-mesityl-10-phenylacridinium tetrafluoroborate (MesAcrPh; **5**, 5 mol %) under blue LED irradiation, which afforded the desired diaziridine **3** in a moderate 40% yield (entry 1) (see Table S1). Inspired by these results, a screen of other commercially available

acridinium catalysts (entries 2 and 3) was completed, with 9-mesityl-3,6-di-*tert*-butyl-10-phenylacridinium tetrafluoroborate (*t*-BuMesAcrPh; **4**) delivering the highest yield. A solvent screen indicated that a mixture of ethyl acetate and acetonitrile (MeCN) in a 1:1 ratio or MeCN and acetone in a 9:1 ratio was required for the acid to be fully soluble. Individual solvents, such as acetone and MeCN, afforded diminished yields (entries 5 and 6). An increase in the catalyst load to 7.5 mol % (entry 7) did not significantly increase the yield (see Table S2). Other organic bases were tested but resulted in poor yields of 15%–27% (entries 8 and 9; see Table S3). Without the presence of blue LEDs (entry 10) or catalyst (entry 11), the reaction did not proceed. Trace amounts of product were detected in the absence of the base (entry 12); however, the vast majority of the acid remained untouched (see Table S4).

Substrate scope

Having developed robust conditions for the photodecarboxylative amination, the substrate scope and functional group tolerance were evaluated (Figure 3). In general, most structural classes of acids were found to be suitable: this includes primary (**9a–9i**), secondary (**10a–10ae**), and tertiary (**11a–11f**) acids. Within these classes, the acids may be cyclic (**10c–10ac, 11a–11c**) or acyclic (**9a–9e, 10a**), benzylic (**10ad, 10ae, 11d**), or contain an α-heteroatom (e.g., N, O) (**9h, 9i, 10d, 10f, 10g, 10j, 10ab, 10ac, 11e, 12b**). The main limitation centered around primary benzylic carboxylic acids: the results were variable and substrate dependent but included low yields (<20%), poor conversions, or complex mixtures. Esters (**9c**) and ketones (**9d, 10e, 10i**) were both tolerated, providing streamlined access into keto-amine building blocks. Olefins (**9e**), aryl halides (**9h**), difluoro-(**10k, 11d**) and trifluoromethyl (**9f**) groups, sulfones (**10p**), lactones (**10y**), and ethers (**9g–9i, 10c, 10f, 10j, 10ab, 11e, 11f**) were suitable. Free alcohols (**10t, 10y**) or phenols (**11e, 12b**), along with silyl-protected derivatives (**10u**), were permissible. Heterocyclic substrates included pyran (**10o**), azetidine (**10d**), tetrahydrofuran (**10f**), piperidine (**3, 10m, 10q–10s, 11a, 12c**), morpholine (**10j**), pyrrolidine (**10g**), benzodioxane (**10ab**), indoline (**10ac**), and chromane (**11e, 12b**). Commonly used nitrogen-protecting groups were well tolerated across the scope and include tosyl (**10d, 10m, 3, 11a, 12c**), Cbz (**10g, 10q, 10ac**), Boc (**10j, 10s**), and acetyl (**10r**). Pharmaceuticals such as naproxen (**10ad**), ibuprofen (**10ae**), and gemfibrozil (**11f**) were converted to the expected diaziridine products in moderate to good yields. The highly complex natural product gibberellic acid was aminated in a modest yield and good d.r. (*ca.* 7.5:1) (**10y**) in the presence of a significant amount of sensitive functionality and steric congestion. Other sterically demanding substrates such as tertiary acids (**11a–11e**) and isopropyl cyclohexane derivative (**10h**) were suitable substrates. The scalability of the method was demonstrated on 1.8 mmol scale for tetrahydrofuran **10f**, giving an 84% isolated yield. Lastly, perfluorinated diazirine **8** successfully reacted with primary (**12a**), secondary (**12c**), and tertiary (**12b**) acids in moderate to good yields. This continues to allow access into the fluorous phase workflow that we elaborated on previously.[27,28]

Synthetic applications

Diaziridines are versatile heterocycles that, under orthogonal conditions, can be converted to amines and hydrazines or applied directly in a growing suite of one-pot or telescoped

heterocycles syntheses.[27] This latter approach leverages the isolable nature of diaziridines and entirely avoids the troublesome handling and purification of free amines and hydrazines. In general, the conversion of diaziridines to amines is accomplished via treatment with mineral acids (e.g., aq. HCl or aq. HI), where the nucleophilic counterion facilitates N–N bond cleavage during the hydrolysis. Alternatively, the heating of diaziridines with methanesulfonic acid (MsOH) or H_2SO_4 in ethanol effects a direct hydrolysis resulting in the hydrazine product. In some cases, treatment with MsOH induced rearrangement to the corresponding hydrazone, which hydrolyzed sluggishly to the desired hydrazines. The addition of aq. HCl (for secondary and tertiary diaziridines) or conc. H_2SO_4 (for primary diaziridines) to these reactions quickly and cleanly completed the conversion to the hydrazines. Irrespective of the diaziridine cleavage employed, the ketone backbone may be recovered and recycled for resynthesis of diazirine reagent **2**.

With these protocols in hand, the problem of the regioselective alkylation of indazoles was considered. The direct N-alkylation of indazole, while often used in medicinal chemistry to interrogate structure-activity relationships around the alkyl group, is plagued by N1/N2 selectivity problems in addition to low yields, particularly with secondary alkyl species, and is entirely unusable for the installation of tertiary alkyl groups.[38] An alternative option is synthesis of the alkyl hydrazine, followed by imine formation and S_NAr with an appropriate electrophile. While this sequence is suitable for target-oriented applications, and indeed has been conducted on process scale, the alkyl hydrazines are required to be synthesized, purified, and isolated in salt form, which often suffers from modest yields.[39,40]

The combination of the diazirine and diaziridine chemistry described above facilitates a medicinal chemistry building-block-style approach (acids + diazirine) to vary the alkyl groups, with a target-oriented approach that guarantees regiochemistry through a hydrazine surrogate and avoids the problems of isolation and purification (diaziridine + electrophile). For the general telescoped synthesis of 1*H*-indazoles, the diaziridine was treated with MsOH to reveal the hydrazine quantitatively; a solvent switch to *N*-methyl-2-pyrrolidine and the addition of electrophile **E1** afforded indazoles **13–20** (see general procedures B and C in the supplemental experimental procedures and Schemes S5 and S6 for more details). Isolated yields are reported from the diaziridine, encompassing three reactions in a telescoped sequence (Figure 4). Electrophile **E1** may be derived from benzene or pyridine (affording azaindazoles) and substituted with acids, halides, trifluoromethyl, or nitro groups, which afford myriad opportunities for downstream synthetic manipulations (e.g., cross-coupling). Further, the carbonyl of the (hetero)arene can be an aldehyde or ketone; in the former case, C3 bromination of the products furnishes a well-precedented diversification handle.[41] Several tertiary examples are shown (**17, 20**) that would be inaccessible through traditional S_N2 approaches. In a similar vein, indazole **18** was recently described as a part of a transcriptional enhanced associate domain (TEAD) P-site binding fragment screening campaign; it, along with several related derivatives, were prepared in 1%–2% yield via alkylation with the appropriate alkyl halides, whereas the diaziridine approach afforded **18** in 53% yield.[42] The cores of a phosphodiesterase-4 (PDE_4)/tumor necrosis factor α inhibitor[39] (**13**) and a tyrosine kinase inhibitor[43] (**14**) were also prepared in 61% and 49% yields from 10n and 9g, respectively.

A net ‘‘single nitrogen transfer’’ telescoped approach was developed for the regioselective synthesis of 2*H*-indazoles. Treatment of diaziridines with HCl in ethanol afforded the corresponding amine *in situ*; a solvent switch to isopropyl alcohol and the addition of aldehyde **E2**, K_2CO_3, and tributylphosphine (via a modified procedure from Genung[44]; see general procedure D in the supplemental experimental procedures and Scheme S7 for more details) effected the condensation-Cadogan cyclization and provided 2*H*-indazoles **21–24** in 55%–69% yield. The diaziridine scope is derived from primary and secondary carboxylic acids, and electrophile **E2** was further substituted with a bromide or methoxy. Notably, 2*H*-indazole **23** is a sub-structure of the core from a retinoic acid receptor-related orphan receptor γ (ROR γ)-modulator developed by Vitae Pharmaceuticals.[45] The reported route uses the parent indazole and an alkylation step from the corresponding tosylate; the desired 2*H*-indazole is isolated in only 10% yield with 47% of the regioisomeric 1*H*-indazole obtained as the major product, highlighting the value of the regioselective diaziridine-based approaches.

Fluoroquinolone antibiotics, such as ciprofloxacin and levofloxacin, are commonly prescribed agents for the treatment of a wide variety of bacterial infections.[46] While many syntheses to the 4-quinolone cores exist, a bis-electrophilic species (e.g., **E3**) is generally preferred for amines that are hindered, complex, or otherwise difficult to engage in alkylation.[47] Carboxylic acids, via the corresponding diaziridines, can now be deployed in these amine-guided routes. 4-Quinolones **25–28** were prepared in a telescoped method by treatment of the diaziridines with HCl, followed by the addition of electrophile **E3** and K_2CO_3 (see general procedure E in the supplemental experimental procedures and Scheme S8). Once the Michael addition was complete, DMF was added and the reaction heated; cyclization via S_NAr delivered the desired products in 58%–79% yield from the corresponding diaziridines. Both secondary and tertiary acids were used, while the electrophiles contained the usual halogenation pattern common to the fluoroquinolone antibiotics.

Mechanism

Using the optimized conditions, the mechanism was probed. A radical trap study was conducted with 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) (1 equiv) as a stoichiometric additive. The TEMPO adduct **30** was observed via liquid chromatography-mass spectrometry (Figure 5A) along with 51% of the diaziridine **10f** (reduced from 91% without TEMPO), suggesting that the reaction proceeds via a radical mechanism (for further mechanistic studies, see Schemes S2–S4); this is in accordance with the previously observed reactivity of diaziridines[27,28] as well as previous literature reports of the photocatalyst.[30–36] A question common to each diazirine amination is the source of the proton required in the termination step of the radical mechanism. 2-Tetrahydrofuroic acid (**29**) was chosen as the model for deuterium-labeling studies (Figure 5B). The reactions were run for 48 h with ^1H nuclear magnetic resonance (NMR) measured at 0, 24, and 48 h (for more details, see Table S5 and Figures S9–S13). Each of the potential proton sources in the reaction was deuterated: acid **29**, acetone, or acetonitrile. A comparison of the N–H peak observed at 3.55 ppm, reported as a percentage of deuterium incorporation (control, no deuterium used, entry 1), showed that the deuteration of the acid results in a disappearance of the N–H

peak (entry 2). Deuteration of both the acid and acetone gives a similar result (entry 3). Using deuterated acetone results in a 78% reduction in N–H peak integration (entry 4), while deuterated acetonitrile has no effect (entry 5). Deuteration of the entire solvent system showed the expected significant incorporation of deuterium into diaziridine **10f** (entry 6). Taken together, the majority of the diaziridine protonation is presumed to originate from the acid, with the balance being abstracted from acetone.

Given both the control and mechanistic experiments described throughout as well as literature precedent, the following mechanism is proposed (Figure 5C).[31,37] Deprotonation of the acid by DBU affords the carboxylate anion (**33**). The excited state catalyst **4*** is reduced via single electron transfer from the carboxylate anion, which promotes decarboxylation to afford alkyl radical **35**. The radical then reacts with diazirine **2** to afford nitrogen-centered diaziridinyl radical **36**. This species is reduced to **37**, simultaneously oxidizing and regenerating catalyst **4**. Based on the NMR studies, the diaziridinyl anion can then accept the proton from DBU (or the free carboxylic acid) or acetone.

In summary, we report the direct, catalytic photodecarboxylative amination of carboxylic acids with diazirines. The mild reaction conditions support a broad functional group tolerance, including ketones, esters, olefins, and alcohols, while allowing for the late-stage amination of complex scaffolds. Several synthetic applications, which leverage the mild, orthogonal conversion of the intermediate diaziridines to amines and hydrazines, demonstrate new telescoped protocols for the regioselective preparations of 1*H*-indazoles, 2*H*-indazoles, and fluoroquinolones. Mechanistic studies suggesta radical mechanism with the diaziridine protonation occurring primarily via a DBU proton shuttle. Further diazirine-based aminations and downstream applications of diaziridines are ongoing in our laboratory and will be reported in due course.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact—Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Justin M. Lopchuk (justin.lopchuk@moffitt.org).

Materials availability—Requests for materials should be addressed to the lead contact.

Data and code availability—All data including experimental procedures, compound characterization data, and stability analysis data are available within the article and its supplemental information file.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Photocatalytic synthesis of aliphatic amines, hydrazines, and N-heterocycles
- Broad functional group tolerance including ketones, alcohols, and olefins
- No pre-functionalization of commercially available carboxylic acids
- Regioselective preparation of 1*H*- or 2*H*-indazoles and fluoroquinolone analogs

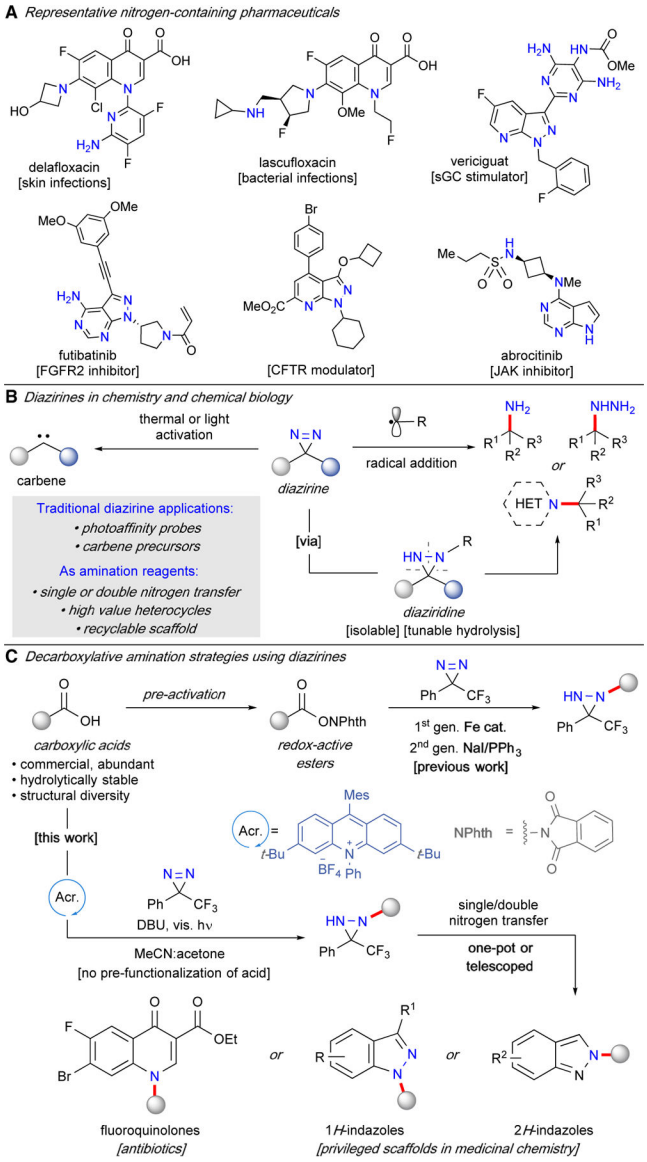
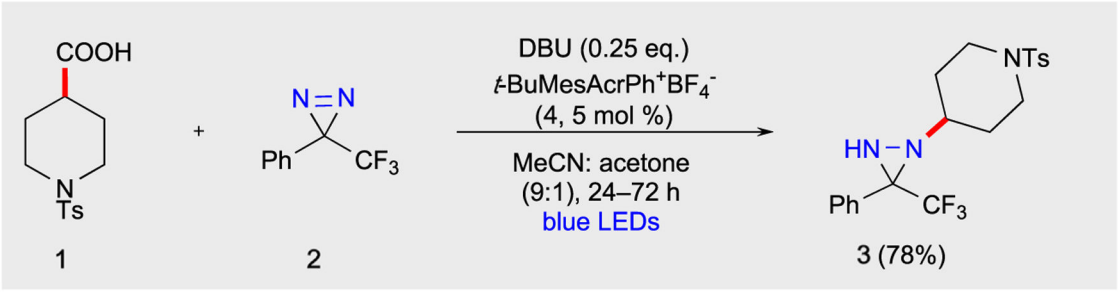


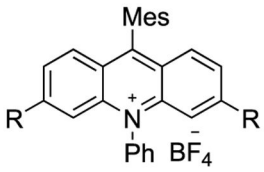
Figure 1. Significance, use of diazirines, and decarboxylative amination strategies

(A) Examples of nitrogen-containing pharmaceuticals.

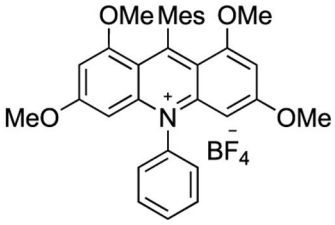
(B) Traditional applications of diazirines in chemistry and chemical biology.

(C) Uses of diazirines in decarboxylative aminations.





4 (R = *t*-Bu)
5 (R = H)



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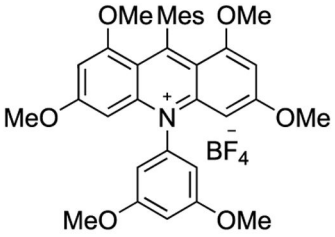


7

Entry	Deviation from above	Yield (%) of 3	Entry	Deviation from above	Yield (%) of 3
1[a]	5 (5 mol%)	40	7[a]	4 (7.5 mol %)	79
2[a]	6 (5 mol %)	45	8	2,6-lutidine	15
3[a]	7 (5 mol %)	trace	9	DABCO	27
4	MeCN:EA (1:1)	76	10	No Light	0
5	Acetone	70	11	No catalyst	0
6	MeCN	60	12	No DBU	trace

Figure 2. Optimization conditions of the photodecarboxylative amination to synthesize compound 3

Reaction conditions: reactions were performed with carboxylic acid **1** (1 equiv), diazirine **2** (1.25 equiv), cat. **4** (5 mol %), and DBU (0.25 equiv) in acetonitrile and acetone (9:1) under blue light irradiation. Yield (%) of **3** refers to isolated yields. **6**, 9-mesityl-1,3,6,8-tetramethoxy-10-phenylacridin-10-ium tetrafluoroborate; **7**, 10-(3,5-dimethoxyphenyl)-1,3,6,8-tetramethoxy-9-(2,4,6-trimethylphenyl)-acridinium tetrafluoroborate; DABCO, 1,4-diazabicyclo[2.2.2]octane. [a]Reactions performed in MeCN:EA (1:1).

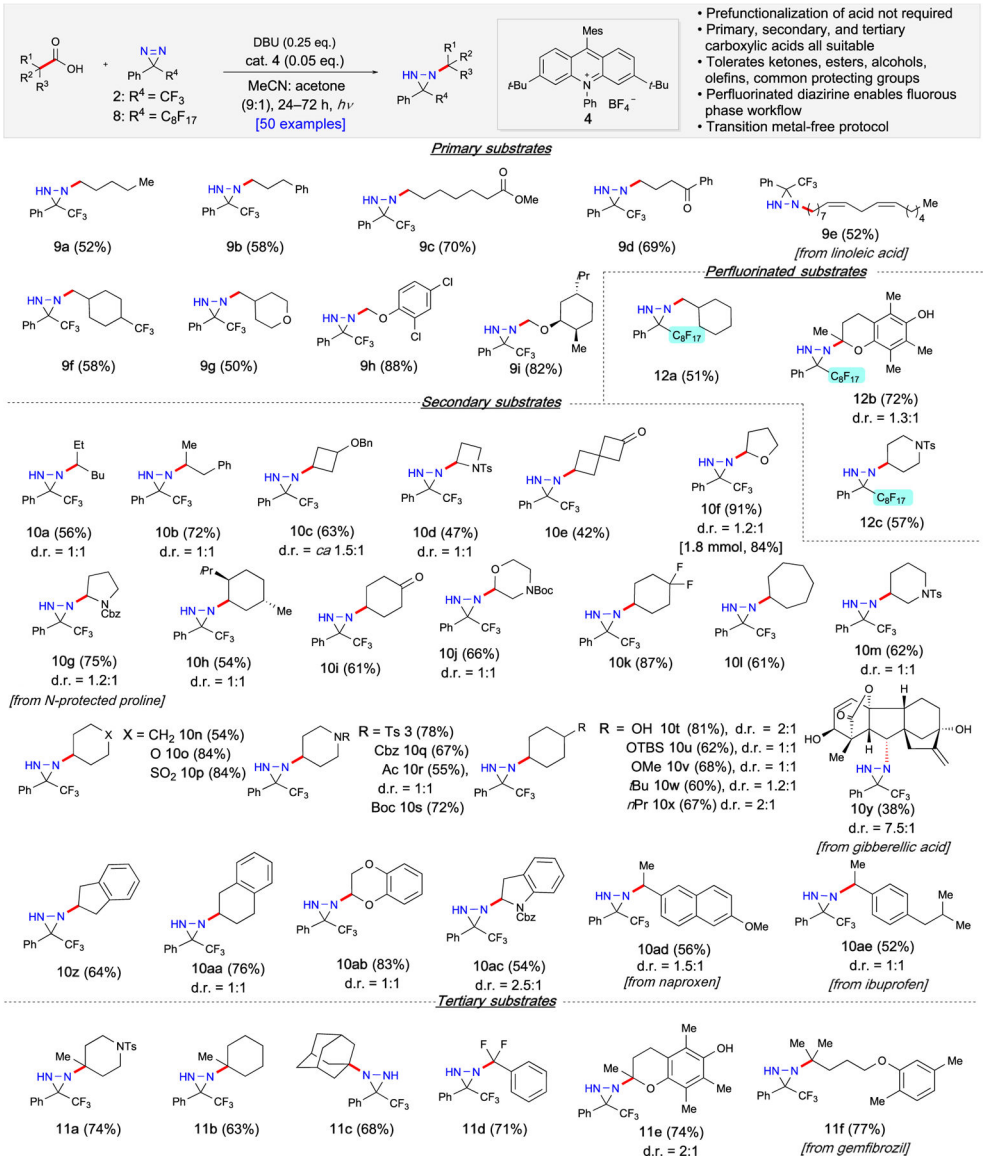


Figure 3. Scope of the photodecarboxylative amination with a variety of carboxylic acids

Reaction conditions: reactions were performed with the corresponding primary, secondary, or tertiary carboxylic acid (1 equiv), diazirine **2** or **8** (1.25 equiv), cat. **4** (5 mol %), and DBU (0.25 equiv) in MeCN and acetone (9:1) under blue light irradiation. Yield (%) refers to isolated yields.

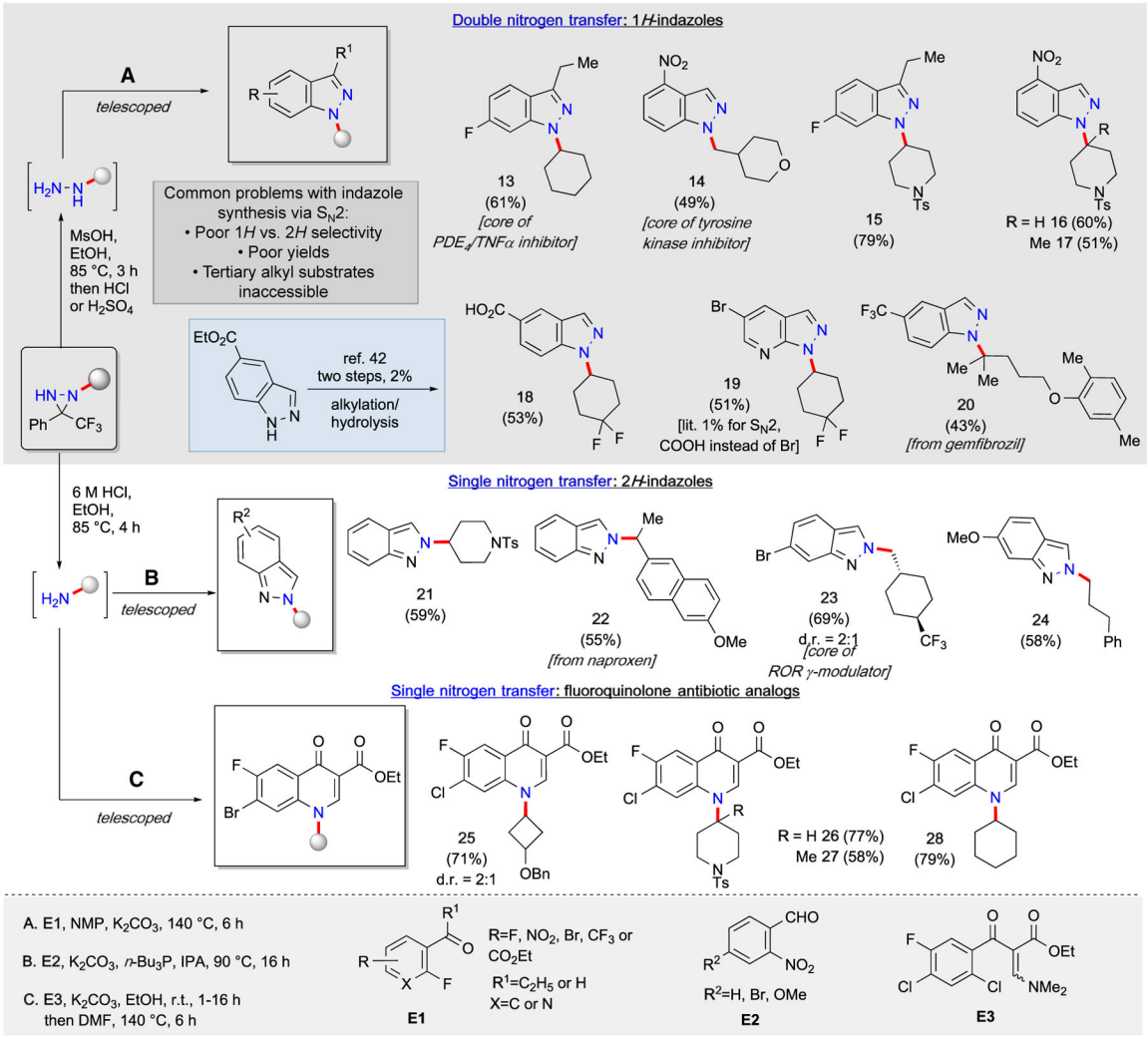
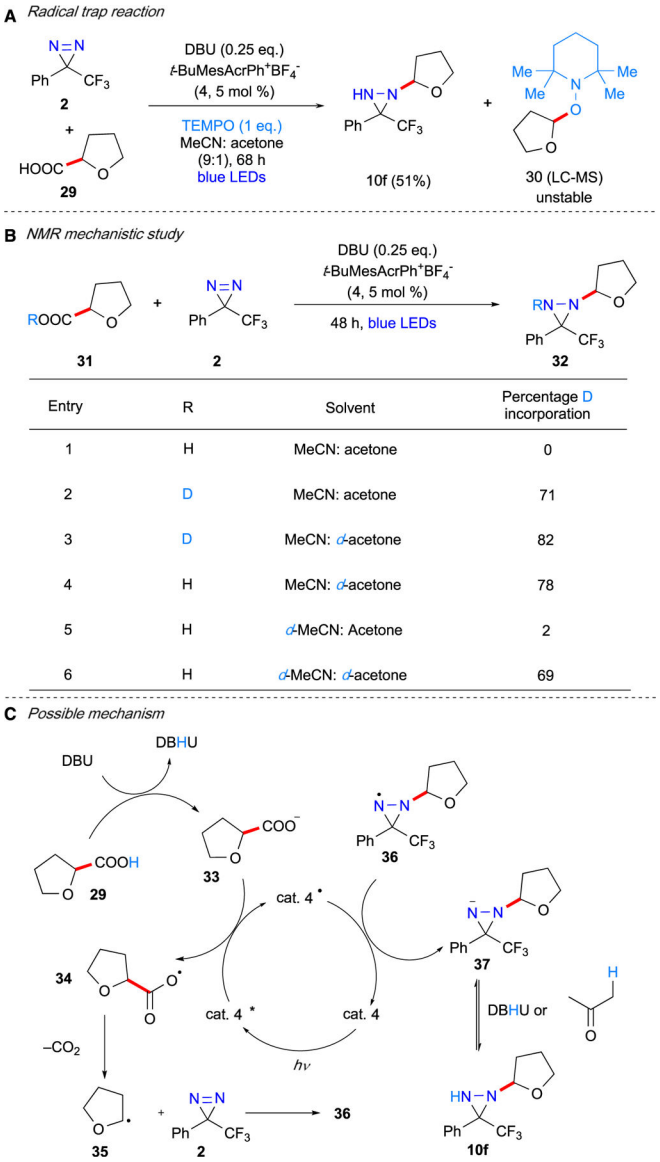


Figure 4. Diversification of diaziridine intermediates for the regioselective telescoped syntheses of 1*H*-indazoles, 2*H*-indazoles, and the fluoroquinolone antibiotic scaffold

(A) General reaction conditions for double nitrogen transfer. 1*H*-indazoles: reactions were performed with the corresponding diaziridine (1 equiv), MsOH (2 equiv), in EtOH (0.1 M) at 85°C for 3h and then 6M HCl (5 equiv) or conc. H_2SO_4 (3 equiv) at 85°C for 12 h followed by *N*-methyl-2-pyrrolidine (NMP; 0.1 M), K_2CO_3 (3 equiv), and **E1** (1 equiv) at 140°C for 6 h.

(B) General reaction conditions for single nitrogen transfer. 2*H*-indazoles: reactions were performed with the corresponding diaziridine (1 equiv), 6 M HCl (4 equiv), in EtOH (0.1 M) at 85°C for 4 h followed by isopropyl alcohol (IPA; 0.1 M) and K_2CO_3 (3 equiv) at 60°C, then **E2** (1 equiv) at 85°C for 4–5 h and *n*-Bu_3P (3 equiv) at 90°C for 16 h.

(C) General reaction conditions for single nitrogen transfer. Fluoroquinolone antibiotic analogs: reactions were performed with the corresponding diaziridine (1 equiv), 6 M HCl (4 equiv), in EtOH (0.1 M) at 85°C overnight and then K_2CO_3 (3 equiv), EtOH, and **E3** (1 equiv) at room temperature for 1–16 h followed by DMF and heating at 140°C.



Entry	R	Solvent	Percentage D incorporation
1	H	MeCN: acetone	0
2	D	MeCN: acetone	71
3	D	MeCN: *d*-acetone	82
4	H	MeCN: *d*-acetone	78
5	H	*d*-MeCN: Acetone	2
6	H	*d*-MeCN: *d*-acetone	69

Figure 5. Mechanistic studies of diaziridine formation via photodecarboxylative amination

(A) Radical trap reaction with diazirine **2**, carboxylic acid **29**, and TEMPO.

(B) NMR mechanistic studies of deuterium incorporation into compound **32**.

(C) Possible mechanism of the photodecarboxylative amination.