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] and 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
*Correspondence: justin.lopchuk@moffitt.org

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.

Introduction

The concise preparation of nitrogen-containing building blocks and the late-stage incorporation of nitrogen onto complex scaffolds is 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 amination approaches,[12-19] 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 (Fig. 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 Ir- and 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 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 (Fig. 1C). The growing toolkit of heterocyclic syntheses is reported with regioselective preparations of 1*H*-indazoles, 2*H*-indazoles, and 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 substrate (Fig. 2). The acid (1 eq.) was treated with diazirine **2** (1.25 eq.) in the presence of the organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.25 eq.) 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 in the SI). 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 yields. A solvent screen indicated that a mixture of ethyl acetate (EA) 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 in the SI). Other organic bases were tested but resulted in poor yields 15-27% (entries 8, and 9, see Table S3 in the SI). 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 in the SI).

Substrate Scope

Having developed robust conditions for the photodecarboxylative amination, the substrate scope and functional group tolerance were evaluated (Fig. 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 the 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 a primary (**12a**), secondary (**12c**), and tertiary (**12b**) acid in moderate to good yields. This continues to allow access into the fluorous phase workflow that we elaborated earlier.[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 (NMP) and addition of electrophile **E1** afforded indazoles **13**-**20** (see general procedures B and C, and Schemes S5-S6, in the SI for more details). Isolated yields are reported *from the diaziridine*, encompassing three reactions in a telescoped sequence (Fig. 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 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 core of a PDE_4/TNFα inhibitor[39] (**13**) and tyrosine kinase inhibitor[43] (**14**) were also prepared in 61% and 49% yield 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 (IPA) and the addition of aldehyde **E2**, K_2CO_3 and tributylphosphine (via a modified procedure from Genung[44], see general procedure D and Scheme S7 in the SI 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 substructure of the core from a 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 with 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 and scheme S8 in the SI). 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 eq.) as a stoichiometric additive. The TEMPO adduct **30** was observed via LC-MS (Fig. 5A) along with 51% of the diaziridine **10f** (reduced from 91% without TEMPO), suggesting the reaction proceeds via a radical mechanism (For further mechanistic studies see Schemes S2-S4 in the SI); 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 (Fig. 5B). The reactions were run for 48 h with ^{1}H NMR measured at 0, 24, and 48 h (For more details see Table S5 and Figures S9-S13 in the SI). Each of the potential proton sources in the reaction were 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 (Fig. 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 suggest a 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

Data Availability

All data including experimental procedures, compound characterization data, and stability analysis data are available within the article and its Supplemental Information file.

Lead Contact and Materials Availability

Requests for materials should be addressed to the lead contact, Justin M. Lopchuk (justin.lopchuk@moffitt.org).

Supplemental Information

Document S1. Supplemental experimental procedures, Data S1-S4, Figures S1-S14, Tables S1-S5, Schemes S1-S8, Notes S1-S14.

Acknowledgements

We gratefully acknowledge the National Science Foundation (CHE-2301063, J.M.L.) for support of this research. This work has also been supported in part by the Chemical Biology Core Facility at the H. Lee Moffitt Cancer Center & Research Institute, an NCI designated Comprehensive Cancer Center (P30-CA076292). We thank

Harshani Lawrence (Moffitt) for NMR and HRMS support and Dr. Zachary Shultz (Moffitt) for assistance with data analysis.

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.

Declarations of Interests

The authors declare no competing interests.

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.

Figure 2. Optimization conditions of the photodecarboxylative amination to synthesize compound 3.
Reaction conditions: Reactions were performed with carboxylic acid **1** (1 eq.), diazirine **2** (1.25 eq.), cat. **4** (5 mol %), DBU (0.25 eq.) 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 eq.), diazirine **2** or **8** (1.25 eq.), cat. **4** (5 mol %), DBU (0.25 eq.) 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 eq.), MsOH (2 eq.), in EtOH (0.1 M) at 85 °C for 3 h then 6M HCl (5 eq.) or conc. H_2SO_4 (3 eq.) at 85 °C for 12 h followed by NMP (0.1 M), K_2CO_3 (3 eq.), **E1** (1 eq.) 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 eq.), 6M HCl (4 eq.), in EtOH (0.1 M) at 85 °C for 4 h followed by IPA (0.1 M), K_2CO_3 (3 eq.) at 60 °C, then **E2** (1 eq.) at 85°C for 4-5 h, and *n*-Bu_3P (3 eq.) 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 eq.), 6M HCl (4 eq.), in EtOH (0.1 M) at 85 °C overnight, then K_2CO_3 (3 eq.), EtOH, and **E3** (1 eq.) at room temperature for 1-16 h followed by DMF and heating at 140 °C.

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.

References

1. Vitaku, E., Smith, D. T., and Njardarson, J. T. (2014). Analysis of the Structural Diversity, Substitution Patterns, and the Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. J. Med. Chem. *57*, 10257-10274. https://doi.org/10.1021/jm501100b

2. Das, P., Delost, M. D., Qureshi, M. H., Smith, D. T., and Njardarson, J. T. (2019). A Survey of the Structures of US FDA Approved Combination Drugs. J. Med. Chem. *62*, 4265-4311. https://doi.org/10.1021/acs.jmedchem.8b01610
3. Flick, A. C., Leverett, C. A., Ding, H. X., McInturff, E., Fink, S. J., Helal, C. J., and O'Donnell, C. J. (2019). Synthetic Approaches to the New Drugs Approved During 2017. J. Med. Chem. *62*, 7340-7382. https://doi.org/10.1021/acs.jmedchem.9b00196
4. Scott, K. A., Qureshi, M. H., Cox, P. B., Marshall, C. M., Bellaire, B. C., Wilcox, M., Stuart, B. A. R., and Njardarson, J. T. (2020). A Structural Analysis of the FDA Green Book-Approved Veterinary Drugs and Roles in Human Medicine. J. Med. Chem. *63*, 15449-15482. https://doi.org/10.1021/acs.jmedchem.0c01502
5. Bhutani, P., Joshi, G., Raja, N., Bachhav, N., Rajanna, P. K., Bhutani, H., Paul, A. T., and Kumar, R. (2021). U.S. FDA Approved Drugs from 2015–June 2020: A Perspective. J. Med. Chem. *64*, 2339-2381. https://dx.doi.org/10.1021/acs.jmedchem.0c01786
6. Lawrence, S. A. (2004). *Amines Synthesis, Properties, Applications*, Cambridge University Press.
7. Bariwal, J., and Van der Eycken, E. (2013). C–N Bond Forming Cross-Coupling Reactions: An Overview. Chem. Soc. Rev. *42*, 9283-9303. https://doi.org/10.1039/c3cs60228a
8. Brown, D. G., and Boström, J. (2016). Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? J. Med. Chem. *59*, 4443-4458. https://doi.org/10.1021/acs.jmedchem.5b01409
9. Trowbridge, A., Walton, S. M., and Gaunt, M. J. (2020). New Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. Chem. Rev. *120*, 2613-2692. https://doi.org/10.1021/acs.chemrev.9b00462
10. Reshi, N. U. D., Saptal, V. B., Beller, M., and Bera, J. K. (2021). Recent Progress in Transition-Metal-Catalyzed Asymmetric Reductive Amination. ACS Catal. *11*, 13809-13837. https://doi.org/10.1021/acscatal.1c04208
11. Ragnarsson, U. (2001). Synthetic Methodology for Alkyl Substituted Hydrazines. Chem. Soc. Rev. *30*, 205-213. https://doi.org/10.1039/b010091a
12. Liang, Y., Zhang, X., and MacMillan, D. W. C. (2018). Decarboxylative sp^3 C–N Coupling via Dual Copper and Photoredox Catalysis. Nature *559*, 83-88. https://doi.org/10.1038/s41586-018-0234-8
13. Yatham, V. R., Belloti, P., and König, B. (2019). Decarboxylative Hydrazination of Unactivated Carboxylic Acids by Cerium Photocatalysis. Chem. Commun. *55*, 3489 - 3492. https://doi.org/10.1039/c9cc00492k
14. Merchant, R. R., Lang, S. B., Yu, T., Zhao, S., Qi, Z., Suzuki, T., and Bao, J. (2020). A General One-Pot Protocol for Hindered *N*-Alkyl Azaheterocycles from Tertiary Carboxylic Acids. Org. Lett. *22*, 4180-4184. https://dx.doi.org/10.1021/acs.orglett.0c01254
15. Kong, D., Moon, P. J., Bsharat, O., and Lundgren, R. J. (2020). Direct Catalytic Decarboxylative Amination of Aryl Acetic Acids. Angew. Chem. *132*, 1329-1335. https://doi.org/10.1002/anie.201912518
16. Li, X., Yuan, X., Hu, J., Li, Y., and Bao, H. (2023). Radical Decarboxylative Carbon–Nitrogen Bond Formation. *Molecules 28*, 4249. https://doi.org/10.3390/molecules28104249
17. Xiong, N., Li, Y., and Zeng, R. (2023). Merging Photoinduced Iron-Catalyzed Decarboxylation with Copper Catalysis for C–N and C–C Couplings. ACS Catal. *13*, 1678-1685. https://doi.org/10.1021/acscatal.2c05293
18. Ding, M., Zhou, S., Yao, S., Zhu, C., Li, W., and Xie, J. (2024). Decarboxylative Amination with Nitroarenes via Synergistic Catalysis. Chin. J. Chem. *42*, 351-355. https://doi.org/10.1002/cjoc.202300493
19. Dong, J., and Yang, Z. (2024). Catalytic One-Pot Reductive Amination of Carboxylic Acids. ChemCatChem e202301427. https://doi.org/10.1002/cctc.202301427
20. Allen, L. J., Cabrera, P. J., Lee, M., and Sanford, M. S. (2014). *N*-Acyloxyphthalimides as Nitrogen Radical Precursors in the Visible Light Photocatalyzed Room Temperature C–H Amination of Arenes and Heteroarenes. J. Am. Chem. Soc. *136*, 5607-5610. https://doi.org/10.1021/ja501906x
21. Zhao, W., Wurz, R. P., Peters, J. C., and Fu, G. C. (2017). Photoinduced, Copper-Catalyzed Decarboxylative C–N Coupling to Generate Protected Amines: An Alternative to the Curtius Rearrangement. J. Am. Chem. Soc. *139*, 12153-12156. https://doi.org/10.1021/jacs.7b07546
22. Zhu, X., He, Z., Li, Q., and Wang, X. (2017). Direct C(sp^2)–H Amination of Aryl Aldehyde-Derived Hydrazones *via* Visible Light Promoted Photoredox Catalysis. RSC Adv. *7*, 25171-25174. https://doi.org/10.1039/c7ra01229b
23. Mao, R., Balon, J., and Hu, X. (2018). Cross-Coupling of Alkyl Redox-Active Esters with Benzophenone Imines: Tandem Photoredox and Copper Catalysis. Angew. Chem. Int. Ed. *57*, 9501-9504. https://doi.org/10.1002/anie.201804873
24. Mao, R., Frey, A., Balon, J., and Hu, X. (2018) Decarboxylative C(sp^3)-N Cross Coupling via Synergetic Photoredox and Copper Catalysis. Nat. Catal. *1*, 120-126. https://doi.org/10.1038/s41929-017-0023-z

25. Chen, K., Wang, Z., and Chen, X. (2020). Photochemical Decarboxylative C(sp^3)–X Coupling Facilitated by Weak Interaction of N-Heterocyclic Carbene. Org. Lett. *22*, 8059-8064. https://doi.org/10.1021/acs.orglett.0c03006
26. Cai, Y., Liu, X., Xu, L., and Shang, M. (2024). Electrochemical Ni-Catalyzed Decarboxylative C(sp^3)–N Cross-Electrophile Coupling. Angew. Chem. Int. Ed. *63*, e202315222. https://doi.org/10.1002/anie.202315222
27. Chandrachud, P. P., Wojtas, L., and Lopchuk, J. M. (2020). Decarboxylative Amination: Diazirines as Single and Double Electrophilic Nitrogen Transfer Reagents. J. Am. Chem. Soc. *142*, 21743-21750. https://doi.org/10.1021/jacs.0c09403
28. Maharaj, V., Chandrachud, P. P., Che, W., Wojtas, L., and Lopchuk, J. M. (2021). Photodecarboxylative Amination of Redox-Active Esters with Diazirines. Org. Lett. *23*, 8838-8842. https://doi.org/10.1021/acs.orglett.1c03344
29. Shu, X., Xu, R., and Liao, S. (2021). Photocatalytic Divergent Decarboxylative Amination: A Metal-Free Access to Aliphatic Amines and Hydrazines. Sci. China Chem. *64*, 1756-1762. https://doi.org/10.1007/s11426-021-1048-4
30. Palkowitz, M. D., Laudadio, G., Kolb, S., Choi, J., Oderinde, M. S., Ewing, T. E., Bolduc, P. N., Chen, T., Zhang, H., Cheng, P. T. W., Zhang, B., Mandler, M. D., Blasczak, V. D., Richter, J. M., Collins, M. R., Schioldager, R. L., Bravo, M., Dhar, T. G. M., Vokits, B., Zhu, Y., Echeverria, P., Poss, M. A., Shaw, S. A., Clementson, S., Petersen, N. N., Mykhailiuk, P. K., and Baran, P. S. (2022). Overcoming Limitations in Decarboxylative Arylation via Ag–Ni Electrocatalysis. J. Am. Chem. Soc. *144*, 17709-17720. https://doi.org/10.1021/jacs.2c08006
31. Fukuzumi, S., and Ohkubo, K. (2014). Organic Synthetic Transformations Using Organic Dyes as Photoredox Catalysts. Org. Biomol. Chem. *12*, 6059-6071. https://doi.org/10.1039/c4ob00843j
32. Griffin, J. D., Zeller, M. A., and Nicewicz, D. A. (2015). Hydrodecarboxylation of Carboxylic and Malonic Acid Derivatives via Organic Photoredox Catalysis: Substrate Scope and Mechanistic Insight. J. Am. Chem. Soc. *137*, 11340-11348. https://doi.org/10.1021/jacs.5b07770
33. Pangu, A. J., Lévesque, F., Roth, H. G., Oliver, S. F., Campeau, L., Nicewicz, D., and DiRocco, D. A. (2016). Acridinium-Based Photocatalysts: A Sustainable Option in Photoredox Catalysis. J. Org. Chem. *81*, 7244-7249. https://doi.org/10.1021/acs.joc.6b01240
34. Margrey, K. A., Czaplyski, W. L., Nicewicz, D. A., and Alexanian, E. J. (2018). A General Strategy for Aliphatic C—H Functionalization Enabled by Organic Photoredox Catalysis. J. Am. Chem. Soc. *140*, 4213-4217. https://doi.org/10.1021/jacs.8b00592
35. White, A. R., Wang, L., and Nicewicz, D. A. (2019). Synthesis and Characterization of Acridinium Dyes for Photoredox Catalysis. Synlett *30*, 827-832. https://doi.org/10.1055/s-0037-1611744
36. MacKenzie, I. A., Wang, L., Onuska, N. P. R., Williams, O. F., Begam, K., Moran, A. M., Dunietz, B. D., and Nicewicz, D. A. (2020). Discovery and Characterization of an Acridine Radical Photoreductant. Nature *580*, 76-80. https://doi.org/10.1038/s41586-020-2131-1
37. Lang, S. B., Cartwright, K. C., Welter, R. S., Locascio, T. M., and Tunge, J. A. (2016). Photocatalytic Aminodecarboxylation of Carboxylic Acids. Eur. J. Org. Chem. 3331-3334. https://doi.org/10.1002/ejoc.201600620
38. Schmidt, A., Beutler, A., and Snovydovych, B. (2008). Recent Advances in the Chemistry of Indazoles. Eur. J. Org. Chem. 4073-4095. https://doi.org/10.1002/ejoc.200800227
39. Caron, S., and Vazquez, E. (2001). The Synthesis of a Selective PDE_4/TNFa Inhibitor. Org. Process Res. Dev. *5*, 587-592. https://doi.org/10.1021/op010223p
40. Ghali, N. I., and Venton, D. L. (1981). A High- Yielding Synthesis of Monoalkylhydrazines. J. Org. Chem. *46*, 5414-5415. https://doi.org/10.1021/jo00339a035
41. Kazzouli, S. E., and Guillaumet, G. (2016). Functionalization of Indazoles by Means of Transition Metal-Catalyzed Cross-Coupling Reactions. Tetrahedron *72*, 6711-6727. https://doi.org/10.1016/j.tet.2016.08.031
42. Heinrich, T., Peterson, C., Schneider, R., Garg, S., Schwarz, D., Gunera, J., Seshire, A., Kötzner, L., Schlesiger, S., Musil, D., Schilke, H., Doerfel, B., Diehl, P., Böpple, P., Lemos, A. R., Sousa, P. M. F., Freire, F., Bandeiras, T. M., Carswell, E., Pearson, N., Sirohi, S., Hooker, M., Trivier, E., Broome, R., Balsiger, A., Crowden, A., Dillon, C., and Wienke, D. (2022). Optimization of TEAD P-Site Binding Fragment Hit In Vivo Active Lead MSC-4106. J. Med. Chem. *65*, 9206-9229. https://doi.org/10.1021/acs.jmedchem.2c00403
43. Boys, M. L., Delisle, R. K., Hicken, E. J., Kennedy, A. L., Mareska, D. A., Marmsater, F. P., Munson, M. C., Newhouse, B., Rast, B., Rizzi, J. P., Rodriguez, M. E., Topalov, G. T., and Zhao, Q. (2012) Array Biopharma, Inc. Substituted N-(1H-Indazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide Compounds as Type III Receptor Tyrosine Kinase Inhibitors. WO 2012/082689 Al.

44. Genung, N. E., Wei, L., and Aspnes, G. E. (2014). Regioselective Synthesis of 2*H*-Indazoles Using a Mild, One-Pot Condensation–Cadogan Reductive Cyclization. Org. Lett. *16*, 3114-3117. https://doi.org/10.1021/ol5012423
45. Claremon, D. A., Dillard, W. L., Fan, Y., Jia, L., Singh, S. B., Tice, C. M., Xu, Z., Yuang, J., and Zhuang, L. (2017). Vitae Pharmaceuticals, Inc. Modulators of ROR-Gamma. WO 2017/087608 Al.
46. Lucia, P. (2012). Quinolones: Synthesis and Antibacterial Activity. In Antimicrobial Agents, National Institute for Chemical-Pharmaceutical Research and Development, pp. 255-272.
47. Dine, I., Mulugeta, E., Melak, Y., and Belete, M. (2023). Recent Advances in the Synthesis of Pharmaceutically Active 4-Quinolone and its Analogues: A Review. RSC Adv. *13*, 8657-8682. https://doi.org/10.1039/d3ra00749a