Decarboxylative Amination: Diazirines as Single and Double Electrophilic Nitrogen Transfer Reagents.

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ABSTRACT: The ubiquity of nitrogen-containing small molecules in medicine necessitates the continued search for improved methods for C–N bond formation. Electrophilic amination often requires a disparate toolkit of reagents whose selection depends on the specific structure and functionality of the substrate to be aminated. Further, many of these reagents are challenging to handle, engage in undesired side reactions, and function only within a narrow scope. Here we report the use of diazirines as practical reagents for the decarboxylative amination of simple and complex redox-active esters. The diaziridines thus produced are readily diversifiable to amines, hydrazines, and nitrogen-containing heterocycles in one step. The reaction has also been applied in fluorous phase synthesis with a perfluorinated diazirine.

INTRODUCTION

The selective transfer of heteroatoms is a powerful tool in organic synthesis that allows for the rapid conversion of inexpensive commercial feedstocks to high value scaffolds for use in medicine, agrochemistry, chemical biology, and materials science.[1] One general class of heteroatom transfer reagents with broad utility are three-membered strained heterocycles (Fig. 1A). Dioxiranes (**1**) are often used for C–H oxidations to afford site-selectivity that is difficult or impossible to match with other methods.[1b] New applications for oxaziridines (**2**) are regularly reported; they are able to transfer either their nitrogen or oxygen depending on the reagent structure and reaction conditions.[2] Both oxaziridiniums and diaziridiniums (**3**) have been more recently developed as practical reagents.[3] Like oxaziridines, they may be used for either oxidation or amination. Diazirines (**4**), which are extensively used as carbene sources in chemical biology,[4] are notably lacking among this series of heterocycles with respect to heteroatom transfer. While scattered reports exist in the literature that demonstrate the ability for diazirines to act as an electrophilic source of nitrogen,[5] it is apparent that none leverage the full potential of these reagents. Given the gap in synthetic methodologies capable of selectively delivering either amines or hydrazines from a single reagent, we investigated diazirines as a potential scaffold for single or double electrophilic nitrogen transfer.

As partly evidenced by their widespread utility in synthetic organic chemistry, chemical biology, and proteomics,[6] diazirines are simple to prepare and their synthesis can be conducted on a relatively large scale that lends itself well to reagent development (Fig. 1B). In principle, the monofunctionalization of diazirine **6** with a carboxylic acid equivalent would afford diaziridine **5**. This structure, while generally stable and isolable, can be converted to amines, hydrazines, and a variety of nitrogen-containing heterocycles. Considered in a retrosynthetic manner, the use of diaziridine intermediates represents a "diversity-enabling disconnection", since diaziridine **5** may be thought of as both a masked amine and masked hydrazine.

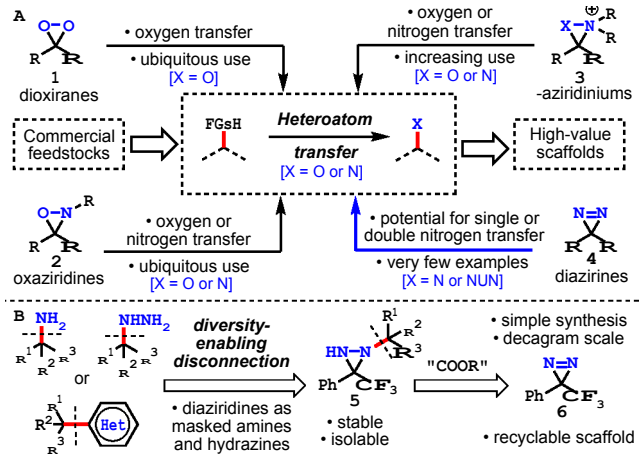

Figure 1. Synthetic methods for strain-release driven heteroatom transfer. A. Heteroatom transfer via three-membered heterocyclic reagents. **B.** Conceptual use of diaziridines as a "diversity-enabling disconnection" in the synthesis of amines, hydrazines, and nitrogen-containing heterocycles.

Herein we report the discovery, development, and application of diazirines as practical electrophilic amination reagents for the synthesis of amines, hydrazines, and nitrogen-containing heterocycles. The use of a perfluorinated diazirine allows entry into fluorous phase chemistry, which both simplifies purification and affords access to the high throughput synthesis of large nitrogen-rich compound libraries critical to drug discovery. This work lays the foundation for a new class of strain-driven reagents that can be used to rapidly forge C–N bonds on simple and complex scaffolds alike.

DEVELOPMENT AND SCOPE

The initial investigation of diazirines as amination reagents was inspired by the work of Krespan and Barton, both of whom found that diazirines could react with alkyl radicals to form imines. Diazirine **7**, upon heating to 165 °C with an excess of cyclohexane (**8**), afforded a modest amount of imine **9** in addition to the typical carbene insertion product **10** (Fig. 2A).[5a] A more detailed study was later reported by Barton, where his eponymous thiohydroxamate ester **11** was found to react with diazirine **6** to afford a mixture of imine **12** and sulfide **13** (Fig. 2B).[5b,5c] Unless a large excess of diazirine **6** was used (twenty equivalents), sulfide **13** was found to be the major product along with low yields of imine **12**. Notably, these precedents lacked both practicality and what we viewed as the critical ability to retain both nitrogen atoms in the initial adduct. Thus, several significant challenges needed to be addressed in order to develop a practical diazirine-based amination: (i) replacement of the photo- and thermally-labile thiohydroxamate ester **11** with a more bench-stable radical precursor, (ii) avoidance of either uncontrolled photochemical conditions or excessive heating that would be expected to convert the diazirine to its corresponding carbene, (iii) reduction of the equivalents of diazirine required from approximately twenty (in Barton's chemistry) to three or less, and, most importantly, (iv) avoidance of imine formation and retention of both nitrogen atoms in the form of a diaziridine intermediate.

Toward this end, N-(acyloxy)phthalimides (e.g. **14**), commonly referred to as redox-active esters (RAE's), were employed as a precursor for the alkyl radicals.[6] RAE's have exploded in popularity in recent years, finding numerous applications in carbon-carbon and carbon-heteroatom bond formation.[7,8] Among the many advantages of RAE's are their simple and rapid preparation from ubiquitous carboxylic acids, ease of purification, and high bench-stability.[9] Furthermore, they may be converted to the corresponding alkyl radicals under either transition-metal catalyzed or photochemical conditions.[7] Despite their obvious advantages, the use of RAE's in C–N bond formation has been limited to several recent reports.[10] Each of these reactions require a tandem photoredox/copper catalyst system to form the C–N bond and all approaches are restricted to the addition of one nitrogen, either via a phthalimide,[10a,10c] primary amine,[10d] or imine.

Exploration of the decarboxylative amination began with nickel-catalyzed conditions employing piperidine-derived RAE **14** with diazirine **6** (Fig. 2C). Diazirine **6** was conveniently prepared in a high-yielding, four-step sequence on decagram scale (Fig. S1).[11] While no amination product was observed with $NiCl_2$-glyme/**18** (entry 1), a 50% yield of diaziridine **15** was obtained with $NiCl_2$•$6H_2O$/**18**. Importantly, no trace of imine **16** was observed in the reaction mixture. In an attempt to improve the yields, the catalyst was changed to $Fe(acac)_3$ and the reaction screened with phosphine ligands (**17**, **19-21**), varying amounts of Zn/TMSCl, and a chlorinated RAE (TCNHPI) (entries 3-9). While the highest yield (76%) was observed with dppBz (**17**), dppb (**21**) was found to be an inexpensive alternative with only a slight decrease in yield. In cases where the RAE was prone to hydrolysis under the reaction conditions, $FeCl_3$•$6H_2O$ was found to increase stability and lead to an improved yield of the diaziridine (entry 6). Critically, the use of diazenes **22** or **23**, perhaps the most commonly used electrophilic amination reagents for the synthesis of hydrazines,[12] in place of diazirine **6** did not afford any corresponding amination products (entries 10-11). Instead, only reduction of the diazenes were observed under various conditions (Table S17). Lastly, contrary to all expectations, similar yields could be obtained without running the reaction under strict precautions, such as an inert atmosphere, anhydrous conditions, or complete elimination of ambient light (72%, entry 12).

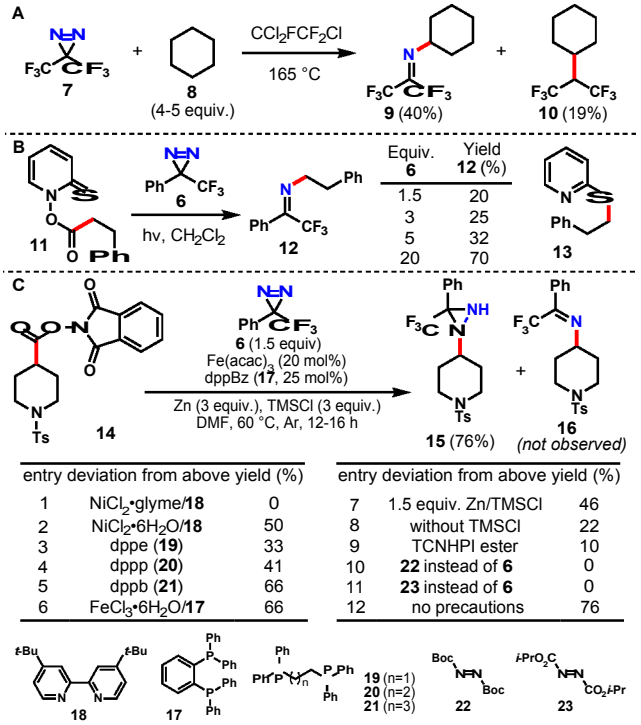

Figure 2. Inspiration and development of the diazirine-based decarboxylative amination. A. Krespan's reaction of diazirine **7** with cyclohexane (**8**). **B.** Barton's reaction of diazirine **6** with thiohydroxamate ester **11**. **C.** Optimization of the reaction of diazirine **6** with redox-active ester **14**. All yields refer to isolated compounds.

With optimized conditions in hand, the scope of the amination was explored with a wide variety of primary, secondary, and tertiary carboxylic acids (Fig. 3). The required RAE's **25** were prepared in generally high yields by treatment of the carboxylic acids **24** with N-hydroxyphthalimide in the presence of N,N'-diisopropylcarbodiimide (DIC) and 4-(dimethylamino)pyridine (DMAP) in multigram quantities.[9] The decarboxylative amination was successful with either cyclic or acyclic hydrocarbons and heterocycles such as tetrahydrofuran (**31**, **48**), piperidine (**15**, **38**, **39**, **41**, **61**), tetrahydropyran (**40**, **55**), tetrahydrothiopyran (**46**), indoline (**52**), and oxetane (**62**). The observed functional group tolerance was quite broad: difluoro (**29**, **43**) and trifluoromethyl groups (**42**), carbamates (**38**, **39**), alcohols (**44**, **58**, **65**), ketones (**45**), sulfones (**46**), ethers (**58**, **63**), esters, (**49**, **53**, **59**), enones (**54**, **65**), olefins (**56**, **58**, **66**), and lactones (**58**) were all tolerated. Highly sterically hindered bonds were formed with relative ease as shown in a menthol derivative **37** and numerous tertiary systems (**60**-**66**). The reaction was also useful for preparing orthogonally protected mixed aminals such as indoline (**52**) and glutamic acid (**53**). The late-stage functionalization of complex natural products and pharmaceuticals was achieved with progesterone (**54**), mycophenolic acid (**58**), gemfibrozil (**63**), glycerrhetinic acid (**65**), and abietic acid (**66**). The reaction was demonstrated both on gram-scale and via a one-pot RAE formation/decarboxylative

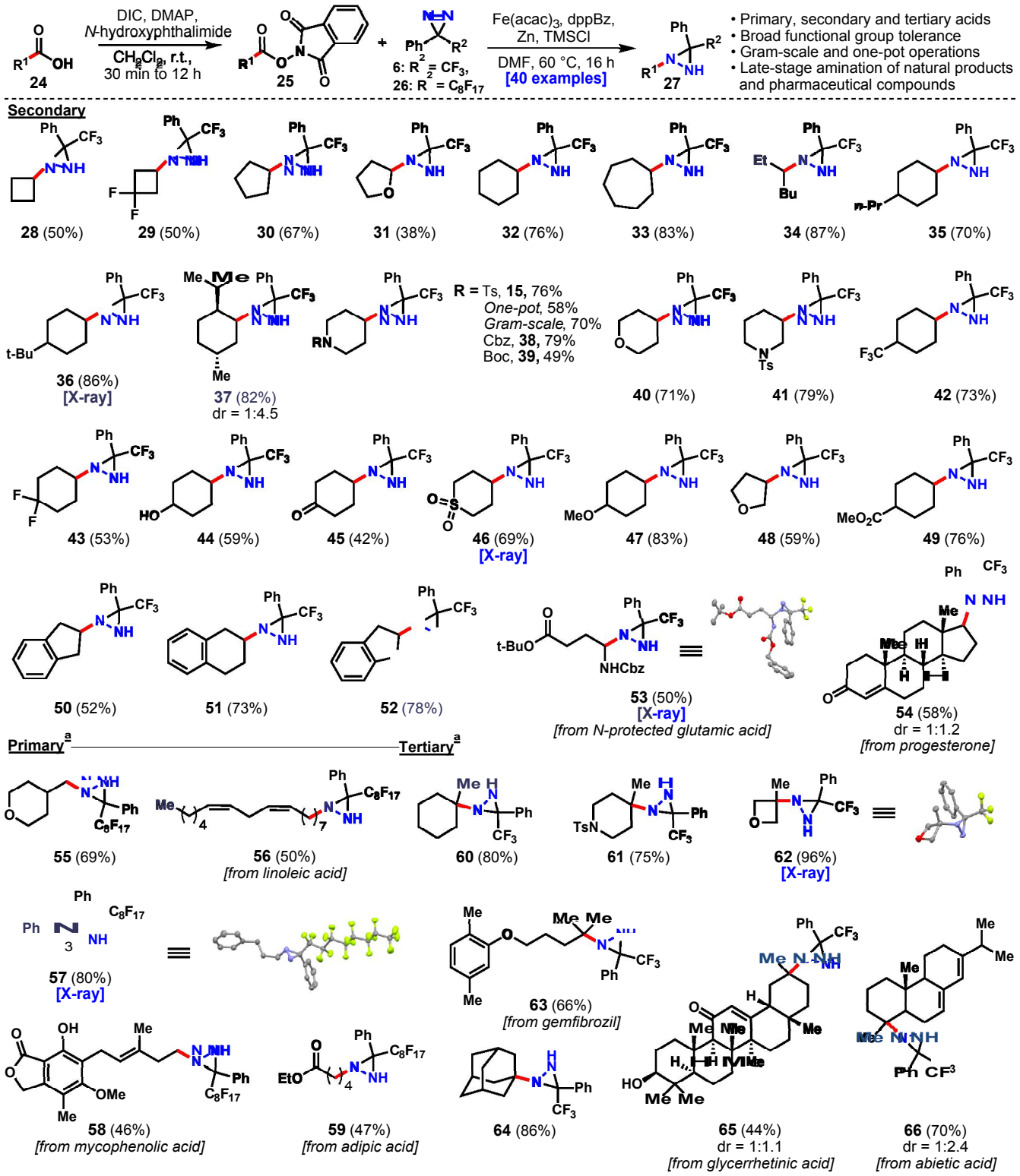

Figure 3. Scope of the decarboxylative amination of redox-active esters with diazirines. Reaction conditions: redox active ester (**25**, 0.1 mmol, 1.0 equiv.), diazirine (**6** or **26**, 1.5 equiv. unless otherwise noted), $Fe(acac)_3$ (20 mol%), dppBz (25 mol%), zinc (3 equiv.), TMSCl (3 equiv.), DMF (0.3 mL), 60 °C, 16 h. All yields refer to isolated compounds. [a]Three equivalents of diazirine were used.

amination sequence in the preparation of piperidine **15** in 70% and 58% yield, respectively (Fig. S21 and S27).

The reaction of primary RAEs with diazirine **6** proved to be challenging. Despite extensive attempts at optimization, including the use of large excesses of diazirine **6**, low yields or no reaction was observed with most substrates. To circumvent this problem, perfluorinated diazirine **26** was synthesized (Fig. S13) and tested under the standard reaction conditions. Gratifyingly, moderate to high yields were obtained for a variety of structurally distinct substrates (**55-59**). Like other transition metal-catalyzed reactions of redox-active esters, this transformation is

presumed to proceed via a radical mechanism, which is supported through trapping experiments with TEMPO (Fig. S35).

DIVERSIFICATION TO AMINES, HYDRAZINES, AND HETEROCYCLES

The utility and diversity of applications of the diazirine-based decarboxylative amination lies in the underexplored versatility of diaziridines (Fig. 4-6). By judicious choice of the reaction conditions, the diaziridine can be selectively hydrolyzed, leaving either one or both nitrogen atoms on the substrate (Fig. 4A).[5d,13] Thus, the diaziridines serve as "masked" amines or hydrazines and obviate the need for the troublesome purification of the highly polar free amines or hydrazines. Treatment of piperidine derivative **15** with MsOH in ethanol effects a hydrolysis reaction to afford hydrazine **67** in 90% yield. Upon purification as the mesylate salt, the yield of the hydrazine drops to 55%, highlighting the utility of the diaziridine approach which avoids the isolation step. Instead, if the acid is coupled with a nucleophilic counterion (e.g. iodide), the hydrolysis occurs with concomitant N–N bond cleavage to afford amine **69**. We have demonstrated fourteen such transformations (**69a-n**) on different substrates to form the corresponding aliphatic amines in excellent yields for most cases (Fig. 4B). For more sensitive functionality (e.g. **69g-h**, **69k-l**, and **69n**), a combination of LiCl/TMSCl may be used to convert the diaziridine to the amine. In each of the cases, ketone **68** can be recovered and recycled into the diazirine reagent synthesis, boosting efficiency and atom-economy. If desired, the amine synthesis can be combined with the decarboxylative amination in one-pot; the addition of LiCl into the initial reaction mixture affords amine **69f** in 63% isolated yield (Fig. 4C).

To further demonstrate the practical utility of the decarboxylative amination, the amine and hydrazine synthesis was then applied to a series of one-pot or telescoped syntheses of various medicinally-relevant heterocycles (Fig. 5). To leverage the one-pot heterocycle synthesis via in situ generation of the amine, N-tosylpiperidine diaziridine **15** was treated with HI in MeCN, followed by addition of the carbonyl or dibromide reagents to afford imidazole **70**,[14] pyrrole **71**,[15] and aziridine **72**,[16] in good yields.

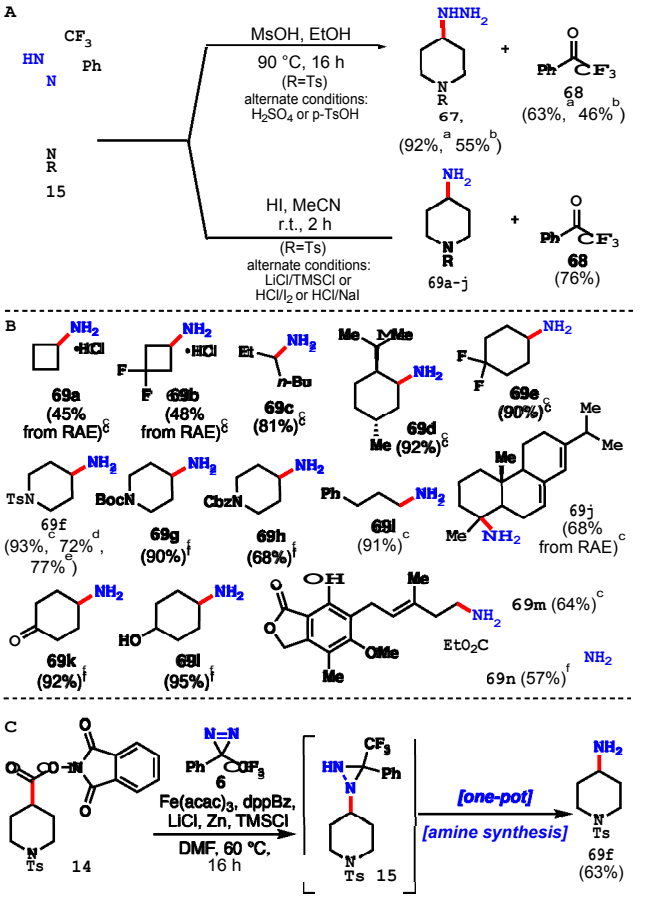

Figure 4. Diversification and one-pot heterocycle synthesis with diaziridines. A. Selective conversion of diaziridines to amines or hydrazines with recovery of ketone **68**. **B.** Aliphatic amines synthesized from the corresponding diaziridines. **C.** One-pot synthesis of amines from diazirines and redox-active esters. Isolated yields are reported. [a]Yield determined by NMR. [b]Isolated yield. [c]HI/MeCN, RT. [d]HCl/I_2, EtOH, RT, 16 h. [e]NaI/HCl, EtOH, RT, 16 h. [f]LiCl/TMSCl, EtOH, 60 °C, 16 h.

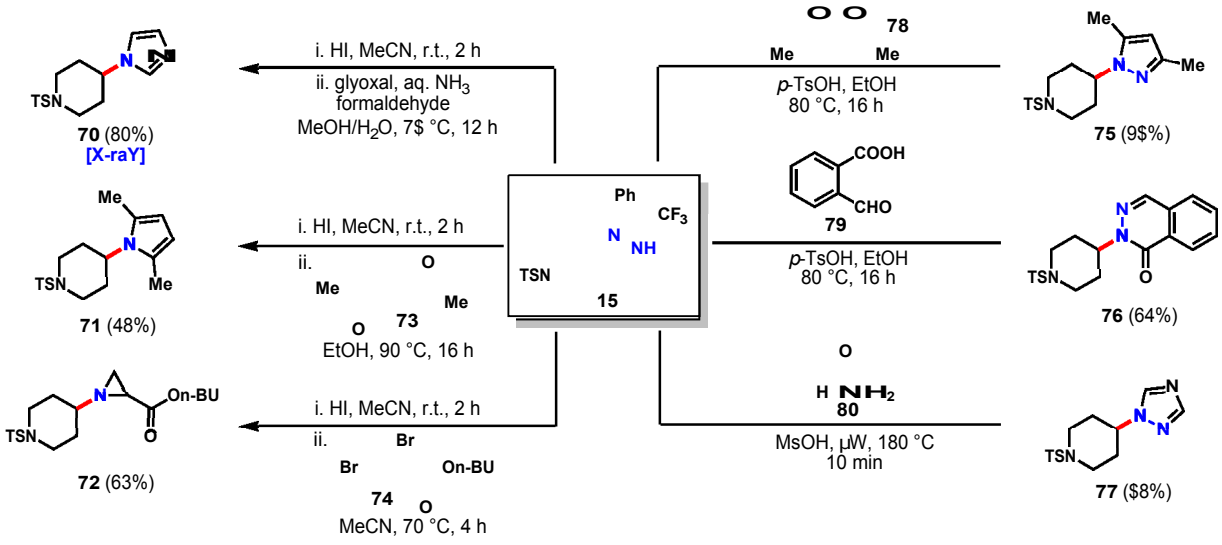

Figure 5. One-pot and telescoped syntheses of pharmaceutically relevant heterocycles from diaziridines.

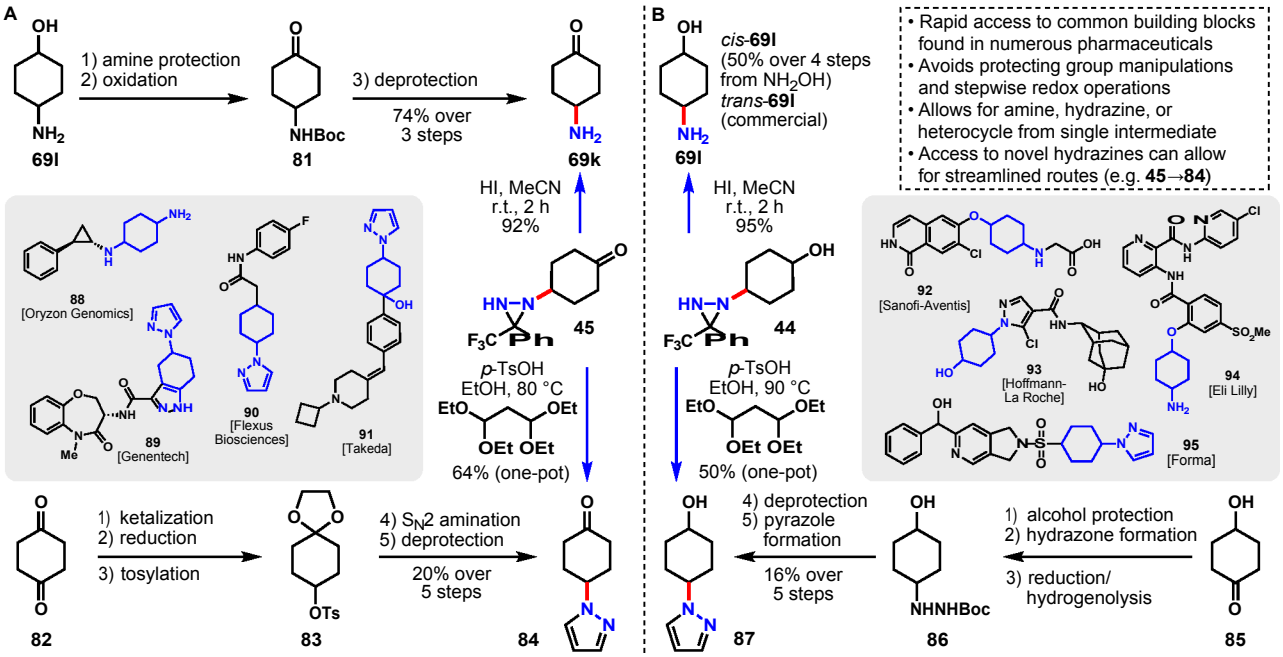

Figure 6. Synthetic applications of diaziridines to pharmaceutically-relevant building blocks. A. Diversification of ketone-containing diaziridine **45** compared to literature methods. **A. Inset.** Pharmaceutical candidates whose synthetic routes required amine **69k** and pyrazole **84**. **B.** Diversification of hydroxy-containing diaziridine **44** compared to literature methods. **B. Inset.** Pharmaceutical candidates whose synthetic routes required amine **69l** and pyrazole **87**.

Alternatively, to prepare heterocycles via the in situ generated hydrazines, N-tosylpiperidine diaziridine **15** was treated with either p-TsOH or MsOH followed by various carbonyl derivatives. In this manner, pyrazole **75** was obtained in 95% yield from 1,3-diketone **78** in the presence of p-TsOH.[5d] Pyridazinone **76** and triazole **77** were obtained in a similar fashion from aldehyde **79**[17] and formamide **80** in 64% and 58% yields, respectively.

With both the diversification reactions and heterocycle-forming protocols in hand, our attention was turned to realizing improved synthetic routes to several commonly employed building blocks in medicinal chemistry: amines **69k** and **69l** and pyrazoles **84** and **87** (Fig. 6). These fragments have been used in the synthesis of numerous pharmaceutical candidates (**88**-**95**, Fig. 6A/B grey insets) spanning therapeutic areas[18] from oncology to the treatment of coagulation disorders. Keto diaziridine **45** was converted to amine **69k** in 92% yield, a compound previously prepared via a sequence of protection, oxidation, and deprotection. The same diazidirine intermediate **45** was also converted to pyrazole **84** in 64% yield. This one pot sequence involves in situ generation of the hydrazine and subsequent reaction with the dialdehyde obtained from 1,1,3,3-tetraethoxypropane. To the best of our knowledge, the hydrazine derived from **45** is unknown in the literature and helps manifest a new route to pyrazole **84**. Previously this compound was prepared from dione **82** through a sequence of monoketalization, reduction of the carbonyl, tosylation, S_N2 displacement with pyrazole, and deprotection, which affords the desired compound in 20% yield over five steps. Furthermore, similar building blocks were obtained through hydroxy diaziridine **44**. In this case, amine **69l** was isolated in 95% yield and pyrazole **87** in 50% yield from diaziridine **44**. Pyazole **87** was made from ketone **85** through a lengthy sequence of protection, hydrazone formation, simultanous reduction of the hydrazone and hydrogenolysis of the benzyl protecting group, deprotection, and ring-formation of the pyrazole (16% over five steps). In summary, this application highlights the diversification potential of diaziridines to amines, hydrazines, and nitrogen-containing heterocycles, the utility of diaziridines as masked amines and hydrazines, and, in some cases, more concise synthetic route alternatives made possible by the use of this method.

APPLICATIONS TO FLUOROUS PHASE CHEMISTRY

Fluorous phase synthesis comprises a family of techniques that were developed to simplify the separation and purification of solution phase reaction mixtures on the basis of fluorine content.[19] Light fluorous phase chemistry requires a perfluorinated "tag" (typically $_{C6F13}$ or $_{C8F17}$) to be attached either to the substrate (often via a protecting group) or the reagent/catalyst.[20] After a given reaction, the perfluorinated molecules are easily separated from the non-perfluorinated components via fluorous solid-phase (F-SPE) extraction or other fluorous chromatographic methods. One of the main challenges in the successful use of fluorous phase synthesis is identifying a suitable site in the substrate or reagents to install the perfluorinated tag that avoids negatively impacting reactivity.[19b] Since the trifluoromethyl group was already successfully embedded in diazirine **6**, we postulated that the switch to the perfluoro group would maintain reactivity, and possibly enhance it. Furthermore, the inherent advantage in using the perfluorinated tag on the diazirine is that it allows for simplified purification in both stages of the amination: synthesis of the diaziridine and conversion to the corresponding amine, hydrazine, or heterocycles.

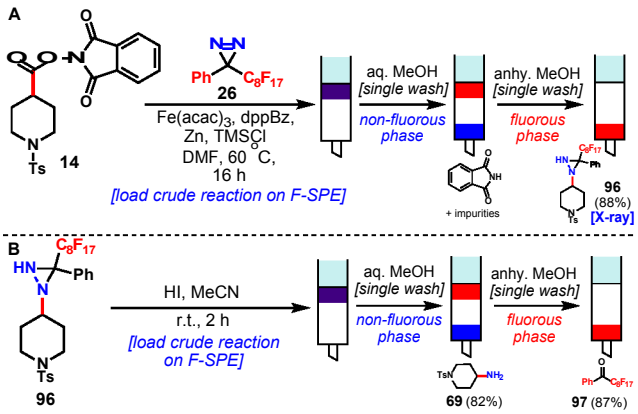

Figure 7. Application of the decarboxylative amination of redox-active esters with diazirines to fluorous phase synthesis. A. Chromatography-free F-SPE synthesis and purification of the diaziridine intermediate **96**. **B.** Chromatography-free F-SPE synthesis and purification of the amine **69f** with concomitant recovery of ketone **97**.

Under the standard reaction conditions, perfluorinated diazirine **26** was found to react smoothly with piperidine-derived RAE **14**. Upon completion of the reaction, the entire crude mixture was applied to the F-SPE cartridge and washed with a single aliquot of aqueous methanol (non-fluorous phase), which eluted all non-fluorous compounds and impurities such as *N*-hydroxyphthalimide and the catalyst/ligand system. A second wash with anhydrous methanol (fluorous phase) afforded pure perfluorinated diaziridine **96** in 88% yield (Fig. 7A). Perfluorinated diaziridine **96** was readily converted to amine **69f** as previously described. Purification under F-SPE conditions furnished amine **69f** in 82% yield in the non-fluorous phase wash, while ketone **97** was recovered in 87% yield in the fluorous phase wash (Fig. 7B). The use of perfluorinated diazirine **26** and its high yielding and high purity conversion to amine **69f** with F-SPE demonstrates proof-of-concept for the use of diazirine-based aminations in high-throughput library synthesis.[21]

CONCLUSIONS

We have demonstrated that diazirines can serve as single and double electrophilic nitrogen transfer reagents in the decarboxylative amination of redox-active esters. The initial reaction affords diaziridines, which are selectively converted in one-pot/telescoped reactions to amines, hydrazines, and various nitrogen-containing heterocycles. The method is suitable for primary, secondary, and tertiary substrates and exhibits a broad functional group tolerance. A perfluorinated diazirine was shown to enable the use of fluorous phase chemistry in both steps of the amination, which allows for the high throughput preparation of nitrogen-rich compound libraries without the need for chromatography. Given the diversity of high-value scaffolds readily accessible through the use of diazirines, these amination reagents are expected to be incorporated by practitioners across research areas in both industrial and academic laboratories. The use of diazirines in reactions beyond the decarboxylative amination is well underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General information, experimental details, stability studies, graphical procedures, and analytical data (^{1}H, ^{13}C, ^{19}F NMR, MS) for all new compounds (PDF)

X-ray crystallographic data are available free of charge from the Cambridge Crystallographic Database Centre (2008713 (**36**), 2008716 (**46**), 2008720 (**53**), CCDC 2008717 (**57**), 2008718 (**62**), 2008715 (**96**), 2008714 (**70**), 2008719 (**S57**)) (CIF)

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Notes

The authors declare no competing interests.

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