Design, Exploitation, and Rational Improvements of Diazirine-Based Universal Polymer Crosslinkers

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Design, Exploitation, and Rational Improvements of Diazirine-Based Universal Polymer Crosslinkers

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CONSPECTUS

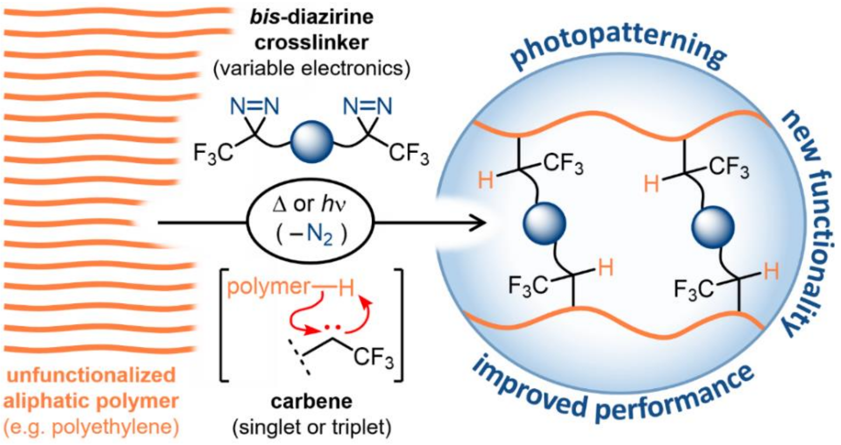
Addition of new covalent bonds between the chains of thermoplastic polymers (i.e. crosslinking) provides improved mechanical strength and enhanced high-temperature performance, while also providing an effective strategy for photopatterning. Traditionally, however, crosslinking of each polymer substrate has required the use of a specific crosslinking technology (hydrosilylation for PDMS, vulcanization for rubber, etc.). The lack of a general solution to the challenge of polymer crosslinking means that there are many thermoplastics (e.g. polypropylene or polyhydroxyalkanoates) that have desirable properties, but which cannot be upgraded by traditional crosslinking technologies.

Our lab developed the first universal crosslinkers for aliphatic polymers by leveraging trifluoromethyl aryl diazirine motifs—functional groups that have been widely used in chemical biology for >30 years, but which had seldom been exploited in materials science. These novel reagents work (via C–H insertion) on essentially any commodity polymer that contains aliphatic C–H bonds, including industrial plastics like polypropylene (the crosslinking of which has been an outstanding challenge in the field for >50 years), as well as commercially important elastomers (e.g. polydimethylsiloxane), biodegradable polymers (e.g. polycaprolactone), and green polymer materials derived from biomass (e.g. polyhydroxyalkanoates).

Subsequent structure–function work from our group led to crosslinkers that were >10-fold more effective in undergoing C–H insertion with aliphatic substrates. We then developed an improved synthesis of our electronically optimized diazirines, and incorporated them into a family of cleavable crosslinker reagents, which permit the on-demand generation of reprocessable thermosets. At the same time, other groups replaced the perfluoropropyl linker in our first-

generation crosslinker with a series of dynamic linkages; these permit the ready generation of vitrimeric materials and can be used in the reactive compatibilization of immiscible plastic waste.

Since the publication of our initial Science paper in 2019, this burgeoning field of diazirine-based polymer crosslinkers has experienced an explosion of interest. Publications from our lab and others have described the use of these reagents in covalent adhesion, photopatterning of low dielectric materials for microelectronics, and direct optical printing of quantum dots. Our crosslinkers have also been shown to heighten the robustness of ice-phobic coatings and improve the performance of woven ballistic fabric, while—perhaps most unexpectedly—substantially improving the stability of high-performance perovskite solar cells. Electronically optimized diazirines can also be used to covalently link proteins to polymer surfaces, suggesting a broad range of applications in biocompatibilization of medical devices. This Account will summarize the development of trifluoromethyl aryl diazirine reagents for materials science, over the past 5 years. A brief comparison will also be made, in the Summary and Outlook section at the end of the Account, to competing (and often complementary) reagents based upon azide and diazoalkyl motifs. Finally, we have compiled a Frequently Asked Questions list that covers many practical aspects of crosslinker design and application; this is appended as Supporting Information.



KEY REFERENCES

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- Musolino, S. F.; Pei, Z.; Bi, L.; DiLabio, G. A.; Wulff, J. E. Structure–Function Relationships in Aryl Diazirines Reveal Optimal Design Features to Maximize C–H Insertion. *Chem. Sci.* **2021**, *12* (36), 12138–12148.[2] This report describes an extensive survey of Hammett relationships in aryl diazirines, leading to the key finding that electron-rich aryl groups engender a 10-fold improvement in C–H insertion yields.
- Musolino, S. F.; Mahbod, M.; Nazir, R.; Bi, L.; Graham, H. A.; Milani, A. S.; Wulff, J. E. Electronically Optimized Diazirine-Based Polymer Crosslinkers. *Polym. Chem.* **2022**, *13* (25), 3833–3839.[3] This report describes the design and testing of a prototypical electronically optimized *bis*-diazirine, which is shown to have significantly improved efficacy for crosslinking of aliphatic polymer substrates.
- Bi, L.; Godwin, B.; Baran, M. J.; Nazir, R.; Wulff, J. E. A Cleavable Crosslinking Strategy for Commodity Polymer Functionalization and Generation of Reprocessable Thermosets. *Angew. Chem. Int. Ed.* **2023**, *62* (30), e202304708.[4] This report presents an improved synthetic route to access electronically optimized diazirines, and describes a method to install cleavable linkages between diazirine warheads. The resulting crosslinkers can be used to prepare reprocessable thermoset materials from mixtures of commodity thermoplastics.

1. BACKGROUND and OBJECTIVES

Introduction of new covalent bonds—crosslinks—between polymer chains dramatically affects the chemical and mechanical properties of the resulting material. By transitioning from thermoplastics (i.e. linear polymers) to thermosets (i.e. network polymers), materials acquire reduced solubility, increased high-temperature stability (due to a reduction in melting enthalpy, and a decrease in material creep) and increased resistance to chemical, biological, and electrical degradation.[5] Many crosslinked polymers are also mechanically stronger than their non-crosslinked counterparts, due to increased storage modulus, tensile strength, and Young's modulus.[5–7] For example, native rubber (a low-melting material with poor mechanical properties) is made into tires using vulcanization: a crosslinking process in which sulfur molecules react in the vicinity of the double bonds present in the rubber polymer (**Figure 1A**).[8] Similarly, linear polydimethylsiloxane (PDMS) is made into high-performance silicone through hydrosilylation (**Figure 1B**) by taking advantage of Si–H bonds in the polymer substrate,[9–11] while cotton is imbued with wrinkle-resistance properties by crosslinking with formaldehyde derivatives (**Figure 1C**) that react with OH groups in the polymer substrate.[12–15] Polymers can also be photopatterned *via* on-demand crosslinking (i.e. negative-tone photopatterning, in which photo-activation leads to crosslinking in areas of the material exposed to light; unexposed areas remain uncrosslinked and are subsequently removed with solvent).[16]

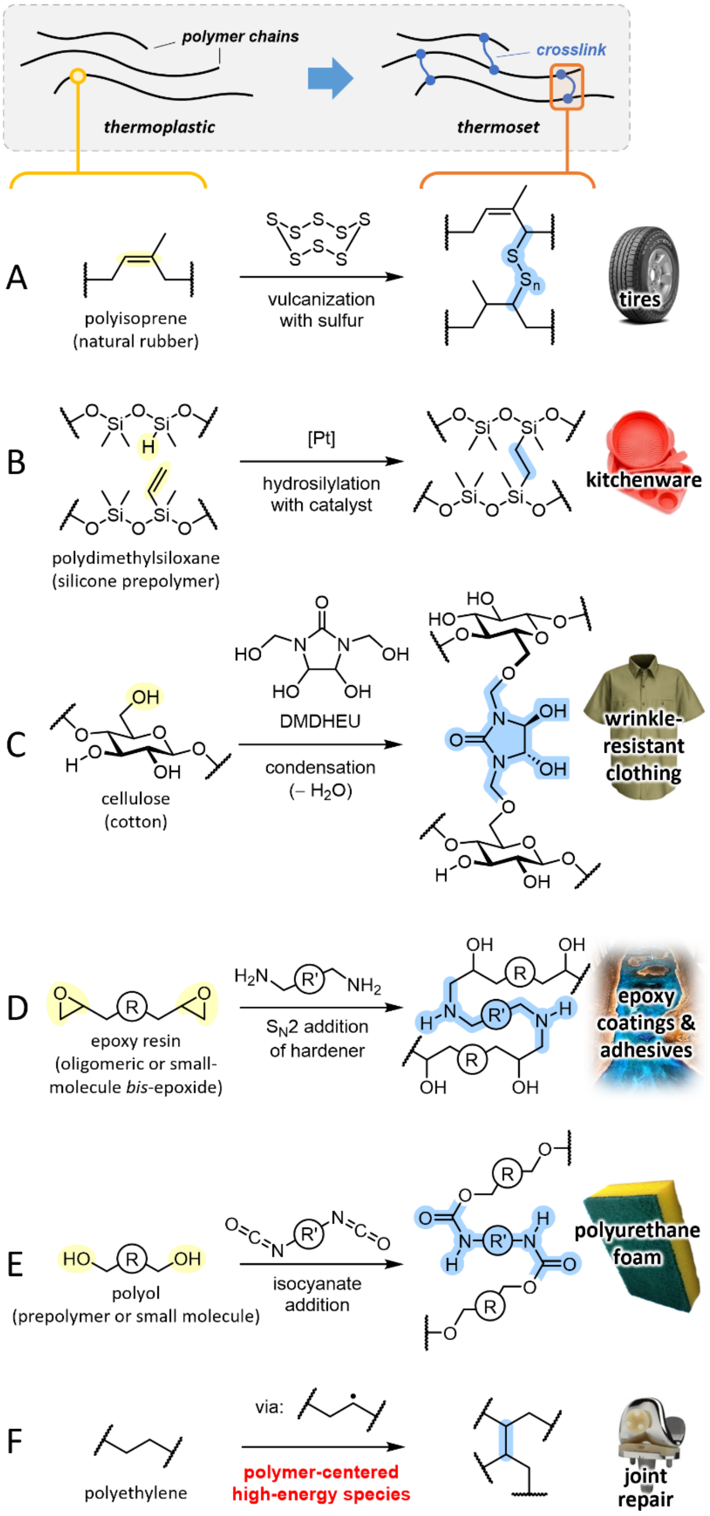


Figure 1. Summary of existing crosslinking technologies.

Polymer crosslinking is economically valuable, but established crosslinking *technologies* are inherently specialized. Vulcanization requires the presence of alkenes present in butadiene rubber (or styrene-butadiene copolymers), hydrosilylation requires the Si–H bonds present in PDMS, and electrophilic formaldehyde derivatives like DMDHEU require the presence of nucleophilic residues on cotton. Similarly, negative-tone photopatterning in the microelectronics industry leverages polymer resists that are equipped with functional groups (often epoxides); secondary polymerization events across these functional groups result in crosslinking between the primary polymer chains.[17,18] In the coatings, adhesives, sealants and elastomers (CASE) industry, crosslinking reactions between resin-bound epoxides and oligoamines (or oligothiols) lead to densely crosslinked networks in epoxies (**Figure 1D**), while crosslinking reactions between poly(ureas) and isocyanates lead to stable polyurethane coatings, sealants, foams, and apparel (**Figure 1E**).[19,20]

Because of the inherent specificity of traditional polymer crosslinking reactions, there exist many useful thermoplastics that *cannot* be crosslinked using standard approaches. For example, while crosslinking in high-density polyethylene (HDPE) is accomplished commercially using radical reactions (**Figure 1F**),[21–23] the existence of competing beta-scission events during radical crosslinking (leading to chain-fragmentation, rather than chain-coupling) means that such methods cannot be ported to other structurally related aliphatic polymers.[24] Prior to the work described herein, therefore, there were no good crosslinking or photopatterning methods for biodegradable or biomass-derived polymers like PCL (polycaprolactone), PLA (polylactic acid), or P3HB (polyhydroxybutyrate). Polypropylene (PP) was established as a particular challenge to the field, since the extra methyl substitution in PP (relative to PE) favors beta-scission through stabilization of the resulting secondary radical.[24,25]

We sought to develop a more general solution to the challenge of crosslinking—and by extension, photopatterning—of low-functionality materials. Our goal was to create a novel suite of crosslinking *reagents* that would work with almost any aliphatic polymer (including unfunctionalized, commodity materials like polyethylene or polypropylene), to make new inter-chain bonds in an on-demand fashion. The implicit challenge, of course, is that because such polymers lack anything that would traditionally be recognized as a functional group (e.g. nucleophilic or electrophilic groups, reactive pi systems, etc.) they are immune to most chemical transformations that would lead to the creation of new covalent bonds.

To address this challenge, we drew inspiration from the chemical biology field, where trifluoromethyl aryl diazirine (TAD) reagents had been used extensively for biological target identification studies.[26,27] The TAD structure was introduced by Brunner, who showed that the parent trifluoromethyl phenyl diazirine (TPD; **1**) could be photolyzed to reveal a reactive carbene, which was sufficiently long-lived to undergo C–H insertion with aliphatic substrate molecules.[28] We hypothesized that by linking two or more TAD units together, we might be able to achieve successive C–H insertions between polymer chains (**Figure 2**).

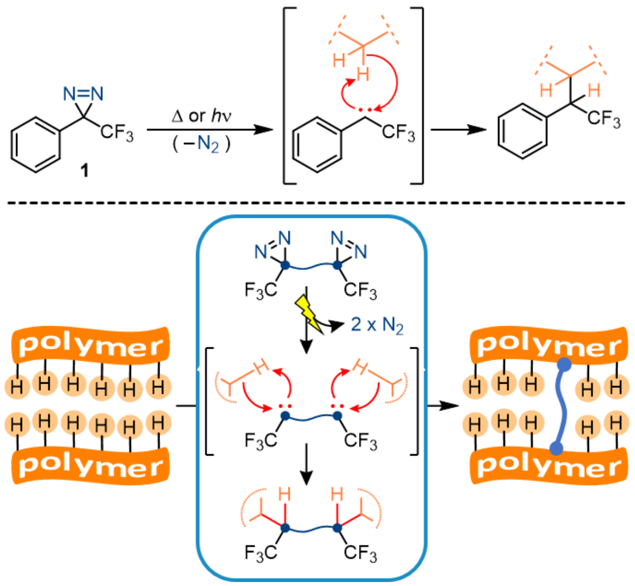


Figure 2. Carbene generation from trifluoromethyl phenyl diazirine (TPD) and proposed utility in polymer crosslinking.

While anticipating several potential challenges to this approach, we were mindful from the outset of the project of three specific advantages that diazirine-based crosslinkers would have, relative to existing crosslinking strategies:

1. ***Broad Generality:*** because essentially every aliphatic polymer (with the exception of Teflon) contains at least *some* C–H bonds that could be sites for insertion, our approach could constitute an almost universal strategy for polymer crosslinking: something that would be in stark contrast to the existing crosslinking technologies outlined above, each of which is restricted to a single polymer class.

2. ***Substrate Fidelity:*** because the high energy species (the carbene) would be localized to the *reagent* rather than to the polymer backbone, there would be no mechanistically obvious pathway for polymer fragmentation reactions to occur—in direct contrast to traditional radical methods, where unwanted beta-scission events may lead to diminishing of desirable polymer properties.

3. ***Topical Application:*** we reasoned that if we could make new covalent bonds between polymer chains, then we should also be able to make new covalent bonds between polymer *surfaces*. This could lead to new opportunities in covalent adhesion for low surface-energy plastics. Moreover, surface treatment would not require the substrate polymer to be solubilized prior to crosslinking.

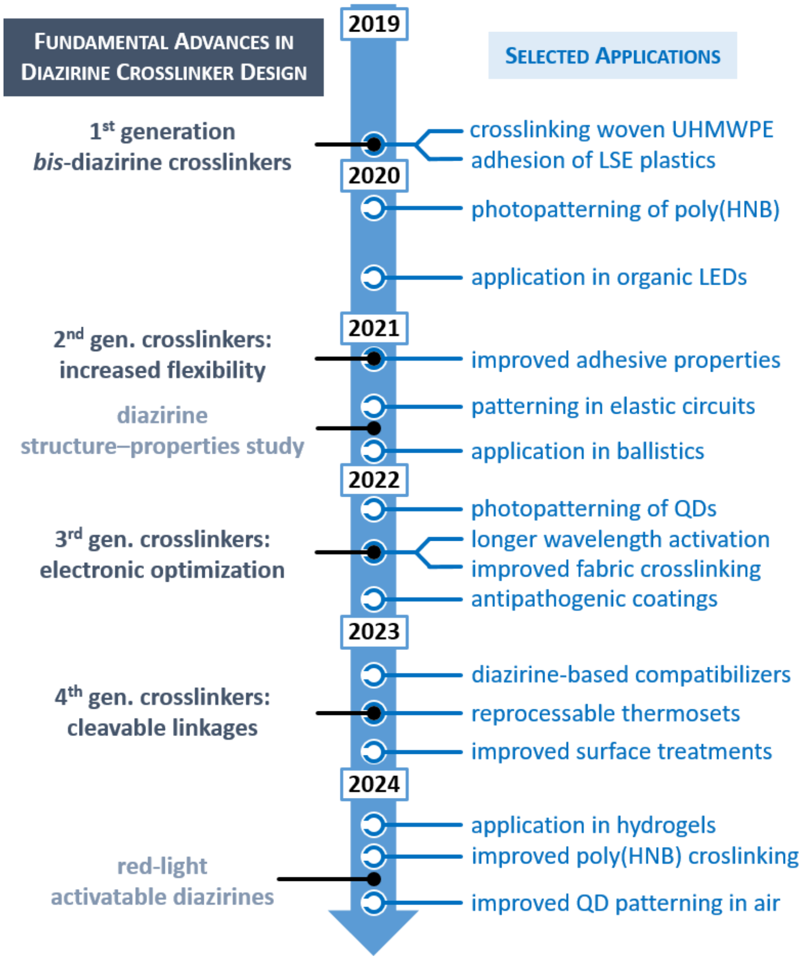


Chart 1. Timeline for the development of TAD crosslinkers. Refer to **Figure S1**

for a graphical summary of the different generations of diazirine crosslinkers.

2. DEVELOPMENT of 1ST GENERATION *bis*-DIAZIRINE CROSSLINKER **4**

Although diazirine-mediated labeling of biological targets (i.e. photo-affinity labeling) is ubiquitous in chemical biology, we were surprised to find that there had been little exploration of TAD reagents in the field of materials science.[29,30] Beginning in 2019, we synthesized and evaluated several candidate *bis*-, *tris*-, and *tetrakis*-diazirines (**Figure 3A**), comparing their ease (and cost) of synthesis, their physical properties (e.g. their volatility or lack thereof, as well as their miscibility with polymer matrices), their ability to crosslink model substrates, and their bench-stability.[1] Aware that the incorporation of two (or more) diazirines into a single molecule may come with a risk of shock sensitivity, we took particular care to characterize each of our compounds according to empirical formulae developed by Yoshida for the safe production of high-energy reagents.[31] We found that the minimal *bis*-diazirine **2** (previously synthesized by the Hayes group[29(a)]) fell above the shock-sensitivity and explosive propagation limits proposed by Yoshida (**Figure 3B**), and so that compound was not pursued further. The pyridine-bridged structure **3** was also explored, since a report from Manetsch and co-workers suggested that an electron-deficient heteroaromatic ring within a TAD group improved handling under ambient light.[32] Regardless, compound **3** fell even further into the predicted danger zone than did **2**, and so neither compound was synthesized on larger scale. Fortunately, additional thermal stability could be engineered into the molecule by simply increasing the molecular weight. We had the best early success with compound **4**, in which two TPD groups were bridged by a perfluoroisopropyl unit.[1] (The extensive fluorination was chosen in part to minimize the likelihood of self-reaction through C–H insertion.) In subsequent work, we evaluated several additional compounds such as those with longer perfluoroalkyl linkers (e.g. **5a** and **5b**),[33] and those with increased rigidity and a larger number of diazirine substituents (e.g. **6**). As illustrated by their placement on the Yoshida plot in **Figure 3B**, compounds **4**–**6**, as well as all subsequent diazirines synthesized in our research program, fall below the shock-sensitivity and explosive-propagation curves, and exhibit no propensity for explosion. Compound **4**, in particular, was put through an extensive barrage of thermomechanical testing (e.g. heating the neat oil above its activation temperature, impact testing by hitting with a hammer, etc.) and no explosive decomposition has ever been observed. In thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) experiments (**Figure 3C**), **4** was observed to cleanly lose an amount of mass equivalent to two molecules of nitrogen gas, and to exhibit an exotherm (at the same temperature as the mass loss) consistent with diazirine activation to the desired carbene.[1]

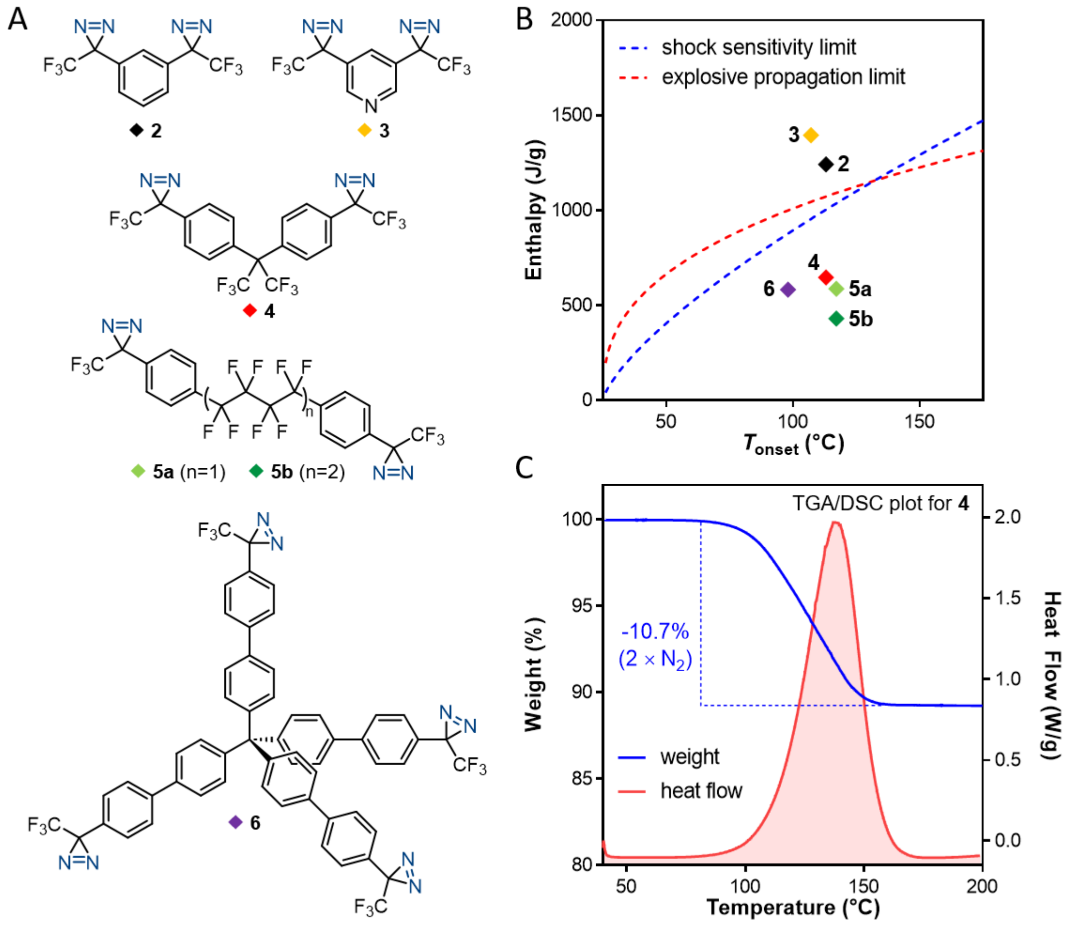


Figure 3. Thermal properties for representative diazirines. A: Structures of diazirines **2**–**6**. B: Yoshida analysis to determine the safety of synthesized compounds **2**–**6**. C: Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) data for compound **4**, showing a clean exotherm and loss of mass consistent with the expulsion of two equivalents of N_2. Panel C adapted from reference 1 with permission from AAAS.

The ability of **4** to crosslink aliphatic substrates was first explored using cyclohexane as a small-molecule surrogate for polyethylene (**Figure 4A**). Successful isolation (proven by ^{1}H and ^{19}F NMR spectroscopy, **Figure 4B**) of the *bis*-cyclohexane adduct **7** confirmed the crosslinking ability of the diazirine reagent.[1] We then used **4** to crosslink several aliphatic polymers (**Figure 4C**), including paraffin wax, polydimethylsiloxane, polycaprolactone, polystyrene, polyisoprene, and polypropylene.[1] The successful crosslinking of polypropylene, demonstrated by showing an increase in the glass transition temperature (T_g) and a decrease in fusion enthalpy correlated with crosslinking density (**Figure 4D**), was particularly significant, given that this substrate is not easily crosslinked using competing radical methods. Subsequent testing of compound **4** revealed it to be non-toxic and non-mutagenic;[34] diazirine **4** also had attractive physical properties, in that it was significantly less volatile than **2** or **3**, and had a melting temperature of +34°C, which meant that it could be weighed out as a crystalline solid, but then applied to polymer surfaces as an oil.[1]

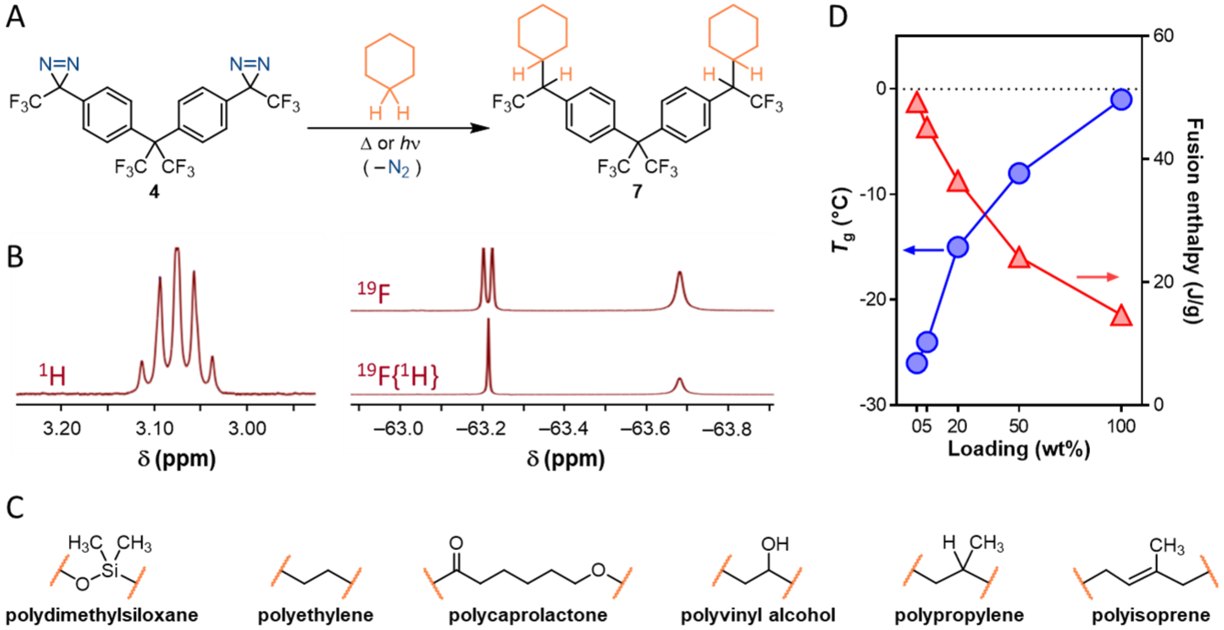


Figure 4. Crosslinking using *bis*-diazirine **4**. A: Crosslinking of cyclohexane, employed as a small-molecule surrogate for polyethylene. B: NMR data confirming the isolation of *bis*-cyclohexane adduct **7**. C: A partial list of aliphatic polymers for which successful crosslinking

has been achieved using diazirine **4**. D: Differential calorimetry data proving crosslinking of PP (blue circles: T_g, red triangles: fusion enthalpy). Panel B adapted from reference 1 with permission from AAAS.

3. SELECTED APPLICATIONS of 1^{ST} GENERATION DIAZIRINE CROSSLINKERS

Following our initial report in 2019 describing the utility of *bis*-diazirine **4** for crosslinking aliphatic polymers, several papers from other groups (as well as a number of studies carried out by our lab in collaboration with others) described the use of *bis*-diazirine reagents for polymer crosslinking and photopatterning applications. For example, a team at Promerus, LLC published a process in 2020 for crosslinking and photopatterning poly(5-hexyl-1-norbornene) (poly(HNB)) using *bis*-(benzyl)diazirine **8** (**Figure 5**).[35] This is a notable achievement, since poly(HNB) contains no functional groups other than C–H and C–C bonds, and would thus be non-patternable using traditional methods. Importantly, the crosslinked polymer maintained a low dielectric constant, when tested at 1 kHz.[35] Somewhat similarly, Pavel Anzenbacher's group published two papers describing the use of *bis*-(phenyl)diazirine **9** for photopatterning of solution-processed polymer LEDs,[36,37] while Deqing Zhang's lab used *tetrakis*-(aryl)diazirine **10** for photopatterning in polymeric semiconductors.[38] In related work, Zhenan Bao's group used *bis*-(benzyl)diazirine **11a**, containing a long lipophilic linker between the two warheads, for photopatterning of high-density elastic circuits intended to interface with the human body,[39] while the groups of Huang and Feng used crosslinkers **12a–c** and **11b** for patterning of organic electrochemical transistors for use as implantable neural interfaces.[40,41]

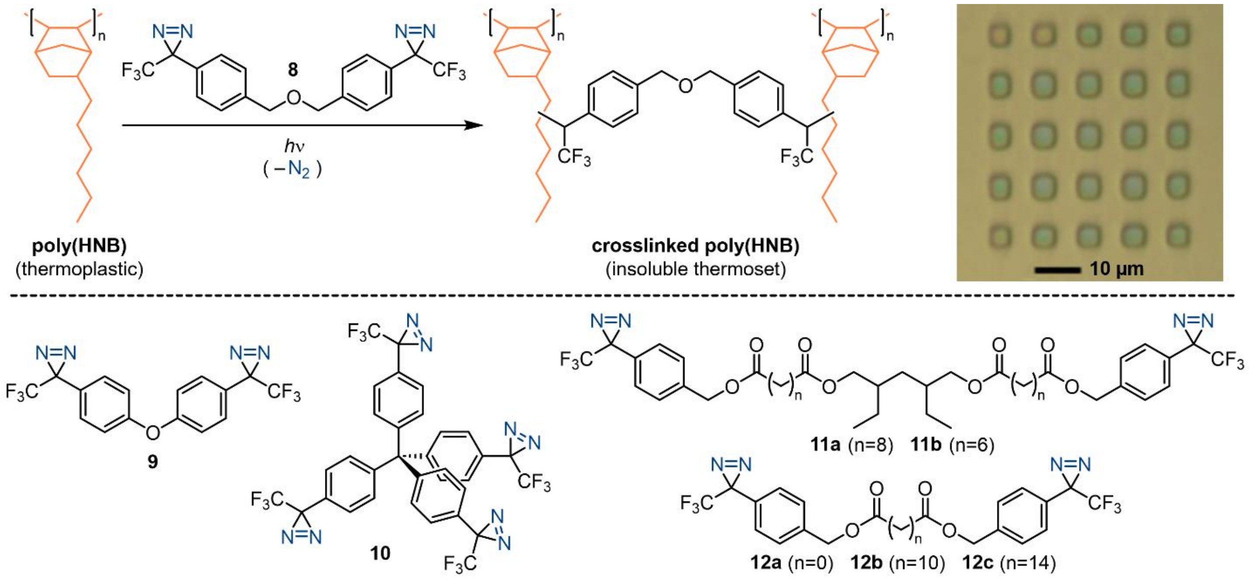


Figure 5. Photopatterning of poly(HNB) using *bis*-diazirine **8**, and selected examples of related *bis*-diazirines that have been used for photopatterning applications in microelectronics (**9**–**12**). For additional recent examples, see references 42–45. Inset photopatterning data adapted from reference 35 with permission from the American Chemical Society.

Perhaps most impressively, a team led by Hao Zhang showed in 2022 that *bis*-diazirine **5a** (a molecule that we originally developed for adhesion applications; *vide infra*) could be used to directly photopattern quantum dots, by crosslinking the lipophilic stabilizing groups on the dot (**Figure 6**).[46] While the patterning efficiency in air was limited through unwanted quenching of the intermediate carbene by atmospheric oxygen (a process that will be discussed in more detail below), this creative application of diazirine-promoted patterning nevertheless represented a significant step forward for the field. The same lab also recently described the optical patterning of perovskite nanocrystals using **5a**.[47]

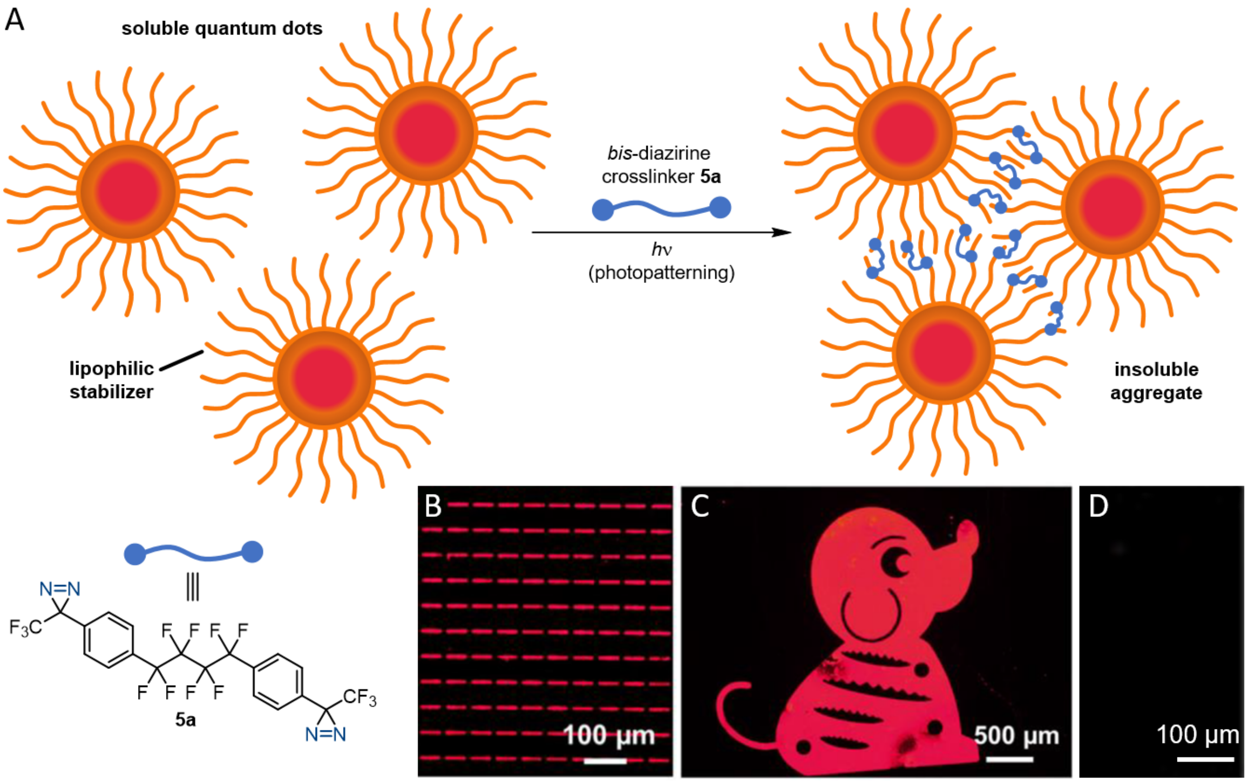


Figure 6. Direct photopatterning of quantum dots using *bis*-diazirine **5a**. A: Crosslinking of lipophilic stabilizing groups leads to photopatterning. B: Regular arrays of quantum dots, printed under N_2. C: Whimsical image printed under N_2. D: Attempted printing under air is unsuccessful, due to quenching of the intermediate carbene by atmospheric O_2. Panels B–D adapted from reference 46 with permission from John Wiley and Sons.

A collaborative team led by Yiqiang Zhan also employed *bis*-diazirine **4** in the formulation of highly stable perovskite solar cells (**Figure 7A**).[48] The proposed mechanism for increased stability involves crosslinking of organic cations by **4**. Perovskites made using **4** had high efficiency as solar collectors (>24%), and were found to be stable for >1,000 hours of continuous operation.[48] By contrast, control perovskites exhibited a rapid decrease in performance.

Diazirine crosslinkers can also be used to upgrade the mechanical performance of commodity materials. Working in collaboration with Abbas Milani's laboratory, we showed that application of **4** to the surface of woven ultra-high molecular weight polyethylene (UHMWPE)—followed by thermal activation to trigger crosslinking—led to improved tear strength.[1] Building upon this result, our team found that multi-layered sheets of crosslinked UHMWPE had superior projectile-stopping ability, compared with non-crosslinked controls (**Figure 7B**).[49] This is a notable result, given the importance of UHMWPE in ballistic-protection apparel. The improved performance was ascribed largely to the presence of inter-fiber crosslinks within the polymer fabric. Moving beyond crosslinking of polyolefins, we also found—in collaboration with Kevin Golovin's group—that diazirine **4** could be used to improve the abrasion resistance of ice-phobic PDMS brushes (**Figure 7C**).[50] The crosslinked surfaces maintained their desired liquidlike behavior, even following multiple rounds of abrasion.

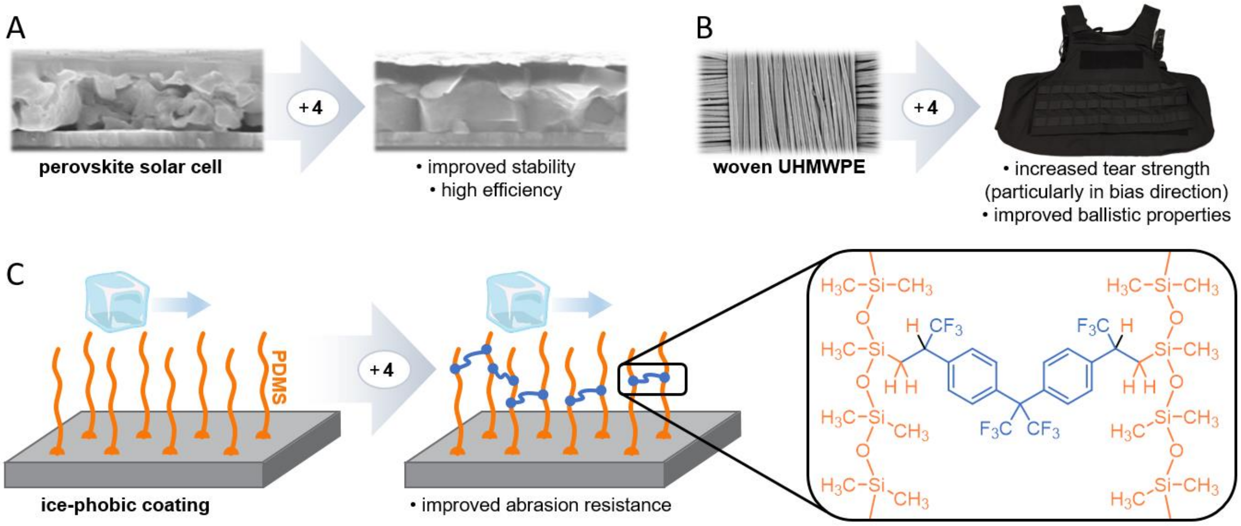


Figure 7. Selected materials science applications for *bis*-diazirine **4**. A: Improvement in perovskite solar cell robustness. B: Improved anti-ballistic performance for crosslinked woven

UHMWPE. C: Improved abrasion resistance for crosslinked liquidlike PDMS brushes. Panels A and C adapted from references 48 and 50 with permission from Elsevier.

4. ADHESION of LOW SURFACE ENERGY MATERIALS:
RISE of 2nd GENERATION CROSSLINKERS and POLY(DIAZIRINE) PRIMERS

Traditional adhesives work through a combination of van der Waals forces, hydrogen bonding interactions, and mechanical interlocking. Adhesive bonding is challenging for low surface energy materials like polyethylene or polypropylene, because the non-polar surface limits polar interactions with the adhesive. We recognized at the outset to our research that *bis*- or *oligo*-diazirines might be able to crosslink two polymer surfaces together through C–H insertion, resulting in strong covalent adhesion. We found that simply painting compound **4** between two pieces of HDPE, then thermally activating to make new bonds across the polymer junction, resulted in adhesive strengths of up to >5 MPa (**Figure 8A**).[1,33] Compounds with longer perfluoroalkyl tethers between the two diazirine warheads (**5a** or **5b**) afforded similar adhesion strength, while providing improved mechanical compliance (**Figure 8B**): a measure of the molecular ‘stretchiness’ in the adhesive bond.[33] Moreover, because the adhesive connection functions through insertion into a C–H bond (and because most aliphatic polymers contain an abundance of these bonds), the protocol was effective for bonding a broad range of substrates. Thus, samples of polypropylene, UHMWPE, poly(methyl methacrylate), and polycarbonate could all be bonded using diazirines **4**, **5a**, and **5b**. Lap-shear samples made from dissimilar materials (e.g. HDPE–polypropylene or UHMWPE–polypropylene) also exhibited strong bonding.[33] In 2022, a team at Facebook (now Meta) filed a patent claiming the use of *bis*-diazirine molecules for adhesion of elastomers used in soft-robotics applications.[51]

Because the additional conformational flexibility in compounds **5a** and **5b** (relative to **4**) contributed to a tougher adhesive bond, we referred to such reagents as 2nd generation crosslinkers.[33]

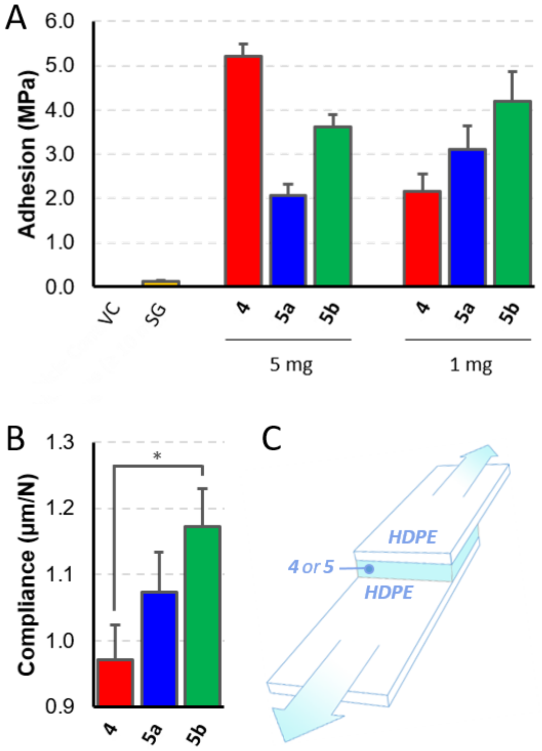


Figure 8. Comparison of rigid crosslinker **4** with conformationally flexible crosslinkers **5a** and **5b**. A: *bis*-Diazirine **4** affords the best adhesion when applied in large amounts, but flexible crosslinkers **5a** and **5b** give better bonding at lower loadings. B: Flexible crosslinkers **5a** and **5b** display improved compliance in the adhesive layer, even in cases where they don't give higher bonding. C: Illustration of the lap-shear setup used to test adhesion. VC = vehicle control. SG = super glue (ethyl cyanoacrylate). Adapted from reference 33 under Creative Commons license.

We also designed a diazirine-enabled *primer* (**13**; **Figure 9**), in which a commodity polyamine (polyethylenimine; PEI) was functionalized with an average of ~10 diazirine groups per polymer chain.[52] Once synthesized, **13** could be applied to lipophilic substrates (either hard plastics or woven polymer fabric), and activated photochemically to drive the formation of new covalent bonds (via C–H insertion) between the primer and the surface.[52] Inter- and intra-primer bonds also form (**Figure S6**), resulting in a thermoplastic-to-thermoset transition within the primer, and presumably helping to support mechanical interlocking with the substrate surface. We could then exploit the remaining nucleophilic groups on the polyamine backbone, applying commodity adhesives (e.g. epoxies, cyanoacrylates, or polyurethanes) that react with amines. This resulted in the construction of extended covalent networks, extending from the surface of one lipophilic polymer, *through* the covalently linked primer, into the commodity adhesive, and then into another piece of primer-bonded lipophilic polymer. Lap-shear samples constructed in this manner displayed considerably enhanced adhesion strength, relative to control samples made without the primer. In the best case, a 950% increase in bonding strength was observed, using polyurethane as the bulk adhesive.[53]

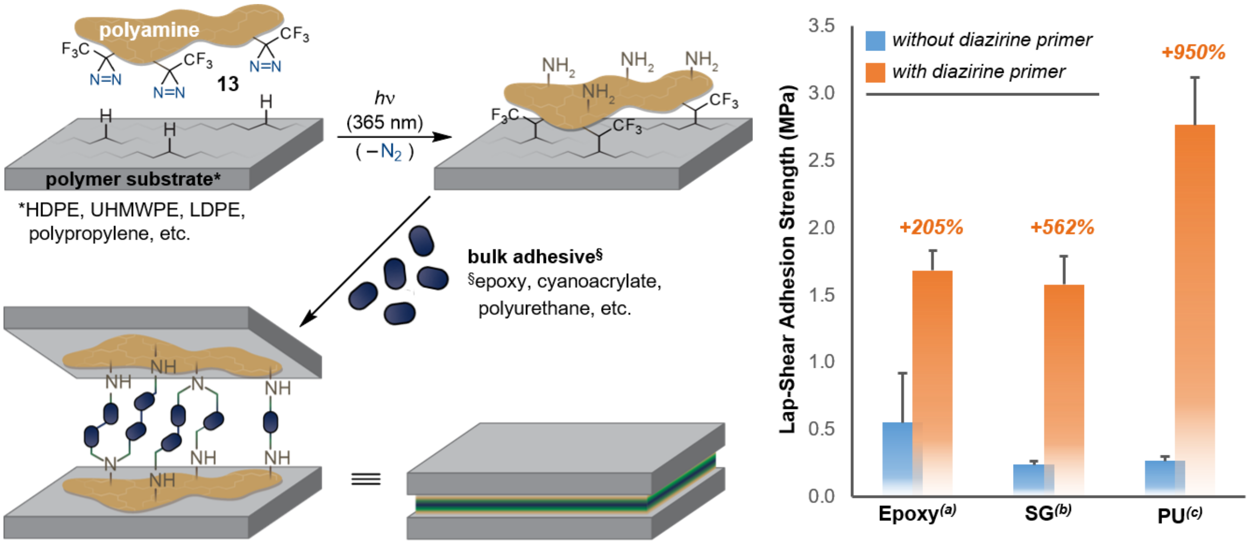


Figure 9. Use of a polyamine–diazirine conjugate as an adhesion primer. [(a)]West System® 105 epoxy resin containing West 205 hardener. [(b)]Gorilla® super glue made with 97% ethyl cyanoacrylate. [(c)]Lepage® PL premium polyurethane. Images adapted with permission from XLYNX Materials.

The presence of the covalently linked amine groups was also exploited to produce UHMWPE-reinforced epoxy composites. Since UHMWPE is significantly lighter than traditional strengthening agents (glass or carbon fiber), its use as a reinforcing material led to lightweight composite materials.[52]

5. SURFACE FUNCTIONALIZATION USING DIAZIRINE REAGENTS

Because diazirine-born carbenes can react directly with the surface of aliphatic polymers, they can provide a convenient platform for surface-functionalization. Working in collaboration with the Buckley, Menon, and Niikura laboratories, we demonstrated that the diazirine–photosensitizer conjugate **14** could be applied to the surface of various commodity materials including melt-blown polypropylene.[54–56] Thermal activation resulted in the formation of new covalent bonds between the small molecule and the polymer surface—establishing a robust linkage between the photosensitizer and the substrate (**Figure 10A**). In the presence of light, the zinc porphyrin photosensitizer contained within **14** can convert atmospheric $^3O_2$ into singlet oxygen: a molecule that is destructive to both viruses and bacteria. We observed the production of $^1O_2$ (**Figure 10B**) from polypropylene surfaces functionalized with **14**, and we could watch in real time as polypropylene samples treated in this way inactivated viral particles that impinged upon the surface (**Figure 10C**).[54] Analogously treated samples were capable of disrupting biofilms formed from both Gram-positive and Gram-negative bacteria (**Figure 10D**).[55,56]

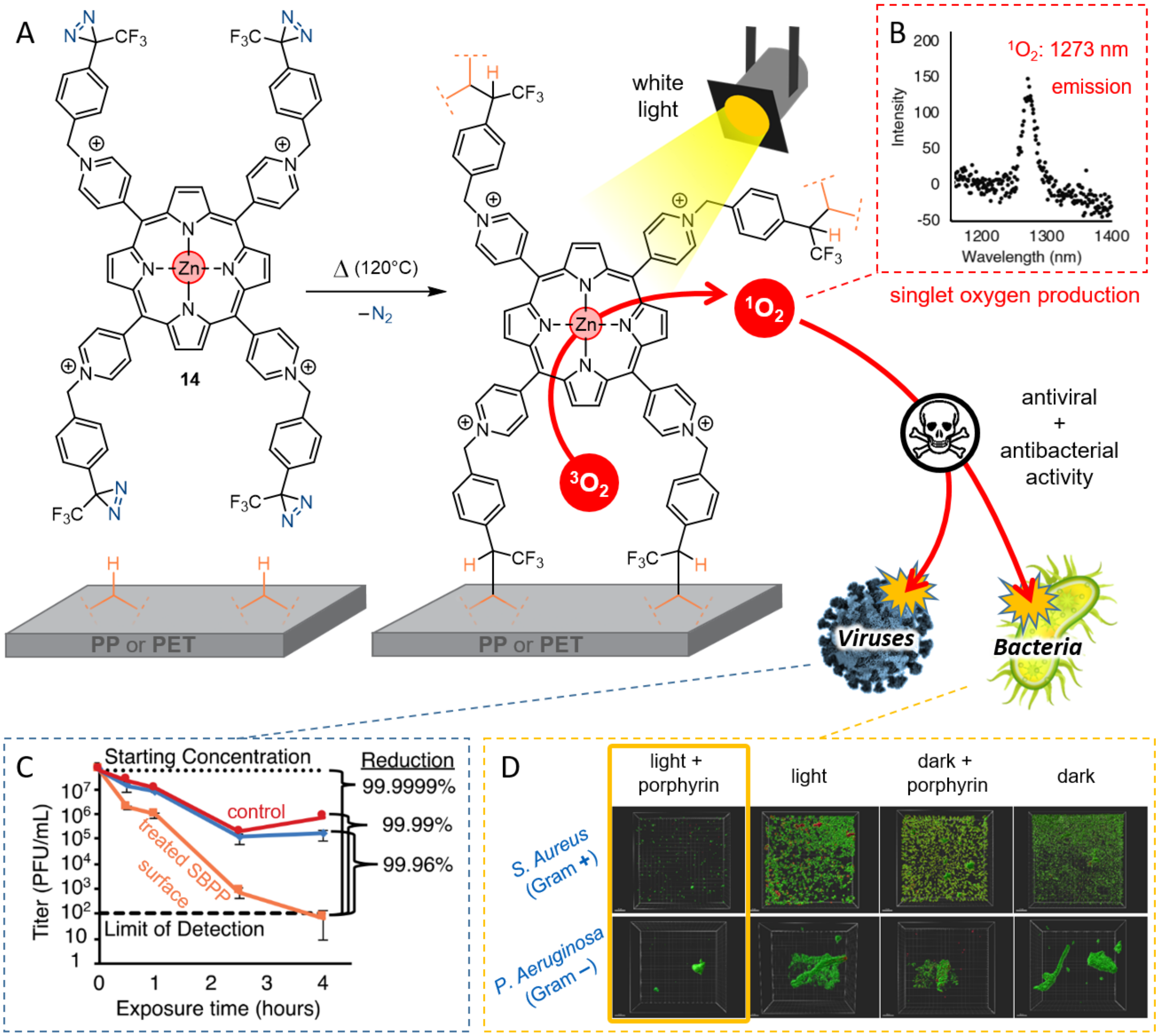


Figure 10. Functionalization of thermoplastic substrates for photodynamic pathogen inactivation. A: Reaction scheme showing the grafting of **14** on a surface, and subsequent light-promoted singlet oxygen ($^1O_2$) generation. B: $^1O_2$ phosphorescence after excitation at 421 nm. C: Log$_{10}$ reduction of PFU/mL active virus vs. exposure time to visible light. D: Confocal microscopy images of biofilms treated (or not) with **14** and/or light. Panels B and C adapted from reference 54 with permission from Springer Nature. Panel D adapted from reference 56 with permission from Elsevier.

6. ELECTRONIC TUNING for IMPROVED DIAZIRINE REAGENTS: DEVELOPMENT OF 3rd GENERATION CROSSLINKERS

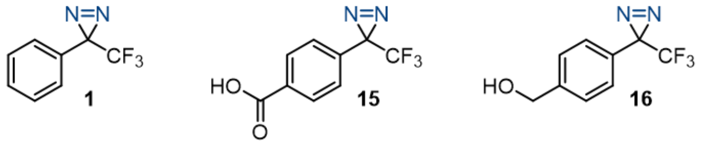
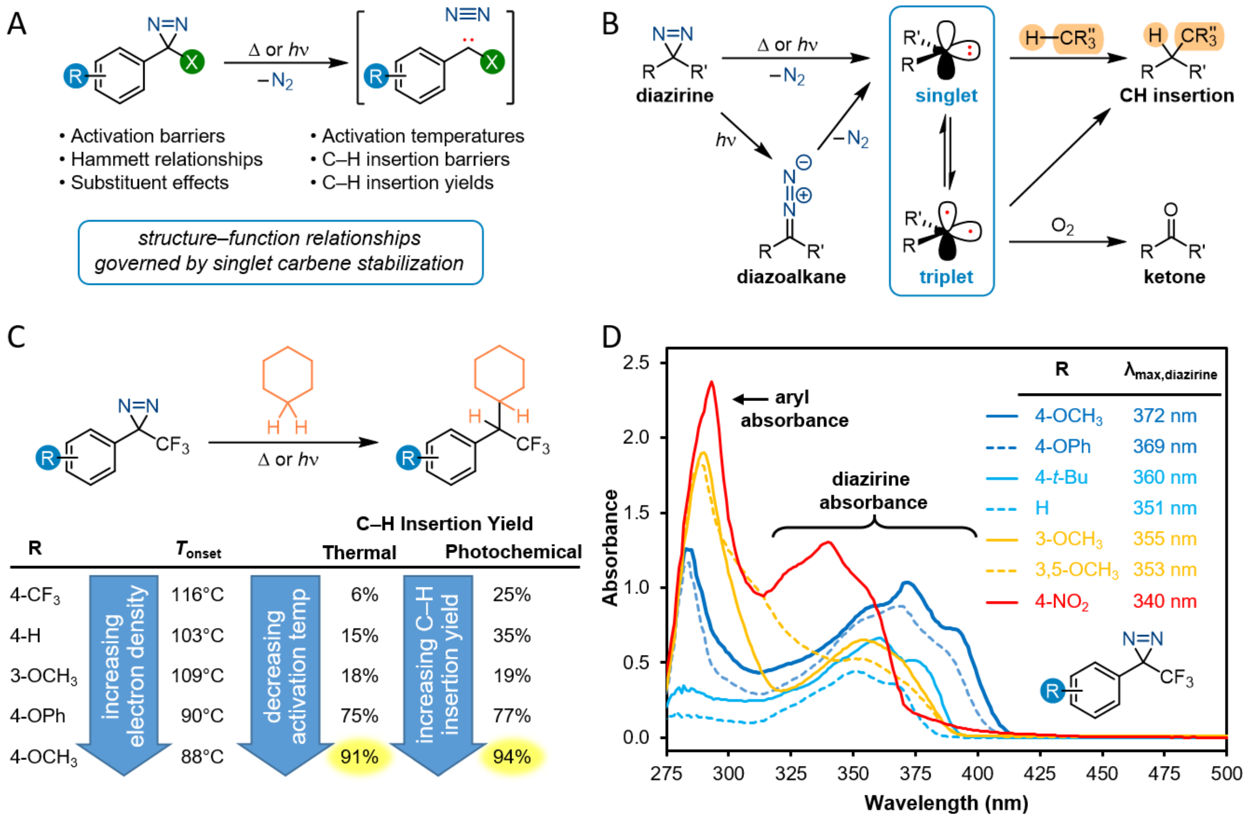


Figure 11. Commercially available diazirine building blocks.

The majority of diazirine-enabled reagents are designed around synthetic expediency, and are therefore built starting either from a commercially available carboxylic acid derivative of TPD (**15**, **Figure 11**) or else from the corresponding benzyl alcohol (**16**). Moving beyond these limited building blocks, we wondered whether changes to the electronic properties of the trifluoromethyl diazirine aryl group might result in improvements to C–H insertion performance, which could be translated into improved efficacy for diazirine-based crosslinkers. Working in collaboration with the DiLabio group, we synthesized a series of monomeric trifluoromethyl aryl diazirines, in which the electronics on the aryl group were systematically varied from electron-poor to electron-rich (**Figure 12A**).[2] We found that more electron-rich diazirines performed far better in C–H insertion experiments with cyclohexane, regardless of whether photochemical or thermal activation was employed. A host of computational and experimental evidence—together with critical earlier findings from the Sheridan[57] and Lindel[58] groups—led to the conclusion that the different outcomes could be largely attributed to the singlet–triplet gaps in the intermediate carbenes.[2] Electron-neutral and electron-poor diazirines are believed to generate singlet carbenes upon initial activation, but these can rapidly relax to the corresponding triplet species, which are lower in energy (**Figure 12B**). Triplet carbenes can engage in C–H insertion reactions (through radical-rebound mechanisms) but they can also be quenched by adventitious O_2. This ‘uses up’ the carbene, resulting in a lower yield of the desired C–H insertion adduct. By contrast, the presence of an electron-rich aryl ring provides a small degree of stabilization to the vacant p-orbital of the singlet carbene—lowering the energy of the singlet (relative to that of the corresponding triplet) enough for it to be the ground state for the carbene intermediate, and yet remain a highly reactive species. The moderately stabilized singlet carbene is largely immune to the presence of oxygen, and can engage in concerted, low-barrier C–H insertion reactions. Very high percent conversions and isolated yields (>90%) were observed, even when cyclohexane was used as the substrate (**Figure 12C**).[2]



R	T_{onset}	C–H Insertion Yield	
		Thermal	Photochemical
4-CF_3	116°C	6%	25%
4-H	103°C	15%	35%
3-OCH_3	109°C	18%	19%
4-OPh	90°C	75%	77%
4-OCH_3	88°C	91%	94%

Figure 12. Structure–properties survey in monomeric aryl diazirines. A: Summary of the study. B: Activation of diazirines to afford singlet or triplet carbenes; singlets are generally preferred for effective C–H insertion. C: Onset temperatures and C–H insertion yields correlate with the degree of electron-richness in the aromatic ring; electron-rich TADs give much higher yields in reaction with cyclohexane. D: Electron-rich TADs also have longer activation wavelengths. Panels B and D adapted from reference 2 under Creative Commons license.

Replacement of the trifluoromethyl group was also examined both computationally and experimentally. Exchanging the CF_3 motif for a methoxy group or halogen (Cl or F) *also* stabilized the singlet carbene following activation, but in these cases the singlet species was *too* stabilized, as a result of positioning a strong pi-donor directly on the carbon that supports the carbene. This resulted in much higher barriers for the desired C–H insertion reaction. The optimal substitution pattern to support effective, high-yielding C–H insertion reactions was therefore identified as encoding a “push-pull” diazirine group, where an electron-withdrawing CF_3 stabilizes the filled orbital of the singlet carbene, and an electron-rich aromatic ring partially stabilizes the vacant p-orbital.

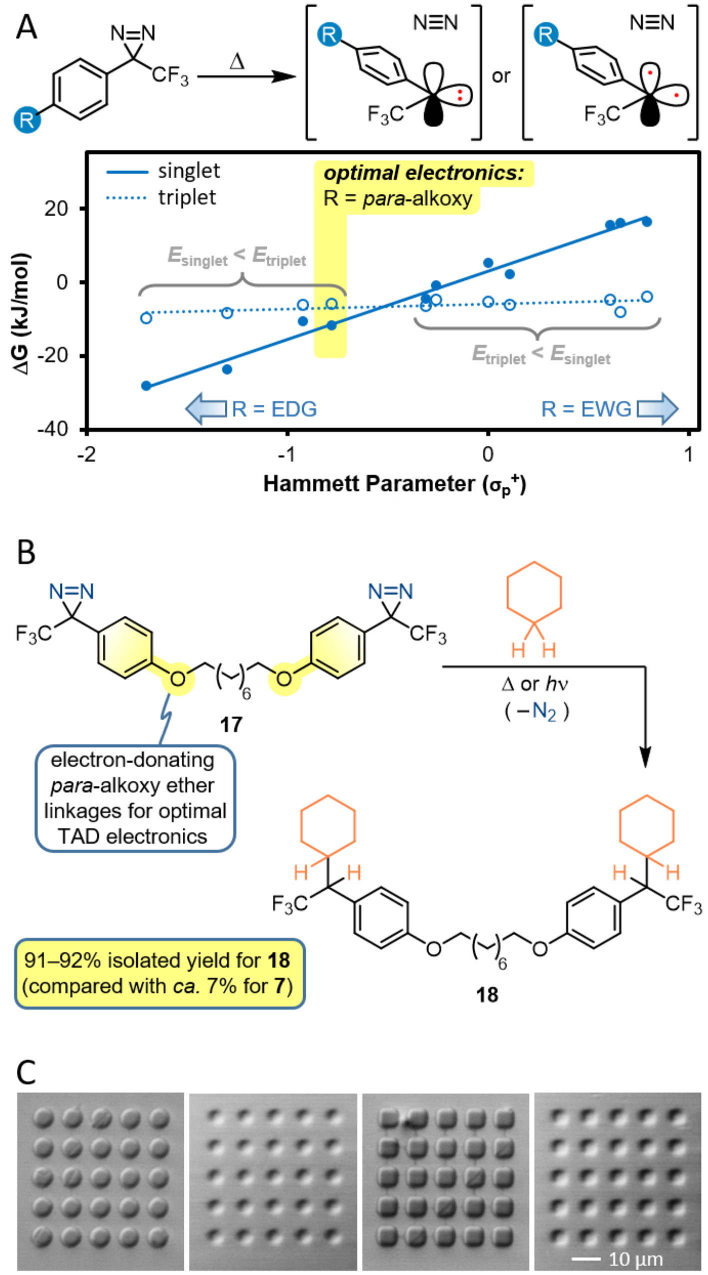


Figure 13. Rational design of a prototypical electronically optimized 3rd generation *bis*-diazirine crosslinker. A: Free energy of reaction (DLPNO-CCSD(T)/cc-pV(D-T)Z CBS//M06-2X-D3/6-31G(d,p)) leading from diazirine starting materials to the corresponding singlet or triplet carbene, for 11 different TADs with varied electronics. A crossover point in singlet vs. triplet energy is revealed, suggesting the optimal use of *para*-alkoxy trifluoromethyl aryl diazirines. B: A prototypical *bis*-(*para*-alkoxy trifluoromethyl aryl diazirine) provides a greatly improved C–H insertion yield for aliphatic substrates. C: Application of crosslinker **17** to the photopatterning of poly(HNB) leads to improved resolution, as well as lower dielectric constant and dielectric dissipation factor. Panels A and C adapted from references 2 and 59 under Creative Commons license.

Building upon these insights, we rationally designed a series of electronically optimized *bis*-diazirines, of which compound **17** served as the prototype (**Figure 13**).[3] The two ether linkages in diazirine **17** render the attached aromatic rings just electron-rich *enough* to make the singlet carbene lower in energy than the corresponding triplet (something that was initially predicted based upon the computational results in **Figure 13A**, where a *para*-alkoxy linkage lies just to the left of the crossover point in the two Hammett plots, and was subsequently confirmed experimentally by collaborators in the de Bruin lab[60]). Remarkably, **17** was able to crosslink cyclohexane in >90% isolated yield, upon application of either thermal or photochemical activation (**Figure 13B**).[3] This represents a >10-fold improvement over the isolated yield for the *bis*-cyclohexane adduct formed from **4**. Working once again with collaborators in the Milani laboratory, we showed that the electronically optimized reagent **17** was much more effective in crosslinking woven UHMWPE fabric, such that the quantity of extractable, unlinked reagent dropped by an order of magnitude. Of equal importance, we observed a direct increase to tensile strength in the crosslinked UHMWPE fabric for the first time.[3,61] Improving tensile strength in UHMWPE fabric is much more challenging than improving tear strength, since the fabric is already extremely strong in the warp and weft directions. In collaboration with lululemon, we also found that we could tunably increase stretch modulus in apparel fabrics,[3] suggesting potential applications in garment customization.

Interestingly, we also found that the temperature for thermal activation of the diazirine group decreased with increasing electron-richness of the aryl ring in a TAD group, while the activation wavelength increased (**Figure 12C**–**D**). Thus, while thermal activation of **4** requires temperatures of ≥110°C, **17** can be activated at 80°C—a significant advantage for many applications. Similarly, whereas **4** (and most other diazirine reagents that are known in the literature) is activated with UV light (~365 nm), **17** can be efficiently activated *either* with UV light *or* using visible-frequency LED light strips operating at 395 nm.[3]

7. SELECTED APPLICATIONS for ELECTRONICALLY OPTIMIZED DIAZIRINES

As described above (**Figure 5**), workers at Promerus had previously demonstrated the use of *bis*-(benzyl)diazirine **8** for crosslinking and photopatterning of poly(HNB).[35] We collaborated with the team at Promerus to conduct a head-to-head comparison of **8**, **4**, and **17**. Together, we found that **17** performed much better than either of the two earlier *bis*-diazirines, affording faster photo-printing speeds (250 mJ/cm^2 compared with ~400 mJ/cm^2 for **8** and ~650 mJ/cm^2 for **4**) as well as improved resolution (**Figure 13C**).[59] Most importantly, poly(HNB) that was crosslinked with **17** maintained a significantly lower dielectric constant *and* dielectric dissipation factor (measured at 10 GHz) than poly(HNB) that was cured with either **4** or **8**.[59] This was true regardless of whether thermal or photochemical activation was employed. Compound **17** also proved more efficacious in helping cured poly(HNB) adhere to a smooth copper film—an important consideration for the creation of printed circuit boards.

We also collaborated with the Zhang lab to test the effect of electronically optimized diazirines like **17**, and found that these permitted photo-patterning to be done *in air*—even for sensitive heavy metal-free quantum dots.[60]

Returning to the concept of surface functionalization (as described above with **14**), we collaborated with the Sask group to show that electrophiles (imidazole carbamates or benzyl halides) could be covalently linked to electronically-optimized diazirines; the resulting conjugates could be used to functionalize the surface of PDMS.[62] The electrophiles were maintained throughout the surface-functionalization step, and could then be used for reactions with antibodies or other proteins—covalently immobilizing these species.[62]

Polymer surface functionalization could also be carried out with an electronically optimized analogue of the polyamine primer shown in **Figure 9**. This optimized form facilitated better curing to UHMWPE fabric, readily transforming the surface from hydrophobic to hydrophilic.[63] Photo-curing of the primer could be done by shining light through a pre-cut mask, allowing the polyamine to be patterned onto the surface. The pattern could be permanently encoded in color, either by thermally degrading the polyamine backbone (resulting in a strong yellow coloring) or by reacting the surface-bound amines with an electrophilic dye.[63] Covalent dyeing of lipophilic fabrics is an important field of research,[64–66] since colorants tend to be polar molecules that will wash out of such materials if they are merely adsorbed onto the surface.[67]

8. REPROCESSABLE THERMOSETS USING DIAZIRINES: 4th GENERATION CROSSLINKERS

Because carbenes that are produced from diazirine reagents can react with any aliphatic C–H bond, *bis*- or oligo-diazirines can readily link together dissimilar plastic materials—as was shown in the adhesion experiments described above. In principle, these reagents could be reacted with mixed plastic waste to bond together two or more types of incompatible polymers into a covalently bound composite. Doing so might allow such waste materials (which otherwise cause significant problems for plastic recycling schemes) to gain a second life. At the same time, crosslinking of any polymer material produces thermosets, which are not generally recyclable themselves, because they cannot be melt processed (although at *low* crosslinking density, a melting transition remains, allowing for some degree of melt processing while still gaining the benefits of crosslinking).

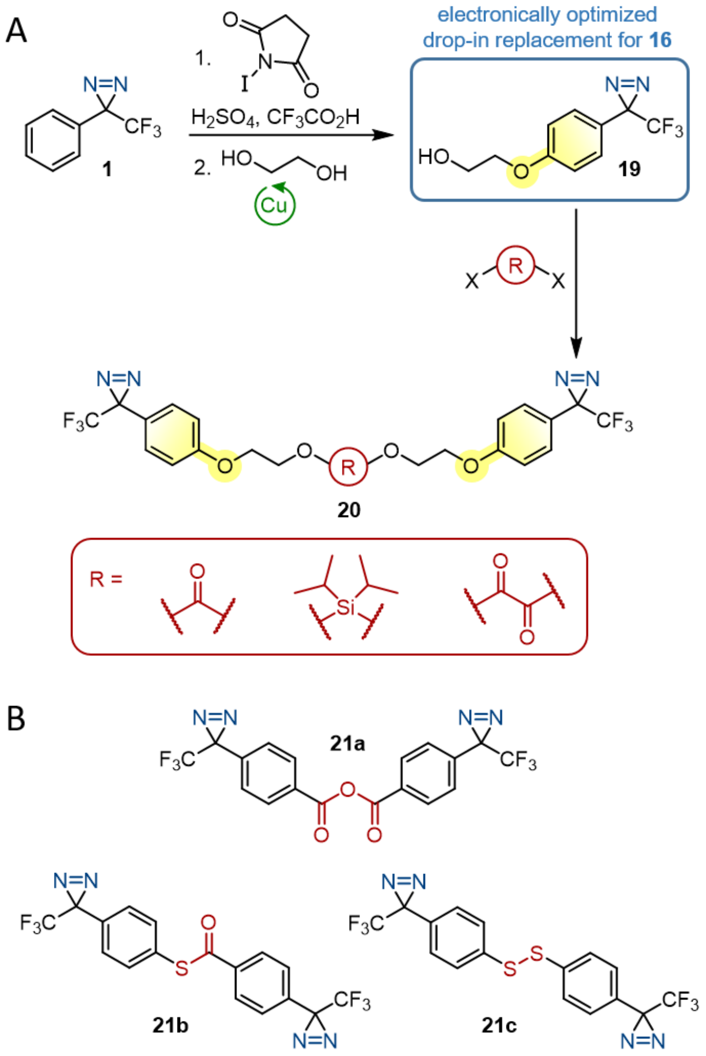


Figure 14. Crosslinkers containing labile covalent bonds. A: Efficient synthesis of a suite of electronically optimized *bis*-diazirines, containing chemically cleavable linkages. Alcohol **19**, accessible in two steps from **1**, is a versatile intermediate. B: *bis*-Diazirines synthesized by the Chen and Rovis groups. The dynamic linkers confer advantages for polymer recycling, and for the compatibilization of mixed plastic waste.[68]

One strategy for creating *reprocessable* thermosets would be to incorporate a cleavable or dynamic linkage between the two diazirine warheads. In this way, polymer substrates (either a single type of polymer, or a mixture of dissimilar plastics) could be crosslinked to form a network polymer, and then during some subsequent processing step the cleavable linkage could be broken, restoring thermoplastic character to the material to support recycling.

We incorporated a series of chemically cleavable linkages (a carbonate, a silyl ether, and an oxalate) into electronically optimized *bis*-diazirines, and used these to prepare crosslinked polyethylene, crosslinked polypropylene, and a crosslinked PE:PP composite (**Figure 14A**).[4] Each of these materials displayed clear rubbery transitions in dynamic mechanical analysis (DMA) experiments, confirming successful crosslinking. Cleavage of the labile linking group restored thermoplastic behavior, as evidenced by the return of a melting transition in the DMA trace.[4] The broken linkage could be restored by adding a suitable electrophile, or else the residual functional group that remained connected to the substrate polymer could be harnessed to add additional surface functionality.

Meanwhile, a team led by Eugene Chen and Tomislav Rovis incorporated dynamic linkages (a thioester, a disulfide, and an anhydride) into *bis*-diazirines **21a–c** (**Figure 14B**) and used these for compatibilization of waste plastic materials, although without optimizing the electronics of the diazirine warhead.[68] The crosslinked material in this case can be viewed as a vitrimer. Most impressively, the team was able to form stable, well-compatibilized composites of lipophilic polyolefins (polyethylene or polypropylene) with polar polyesters (PLLA and PHB). The authors were even successful in producing a ternary blend of three mutually incompatible materials: LDPE:*i*PP:PLLA. The presence of the dynamic linkage allows the crosslinked composite materials to be reprocessed using standard extrusion techniques.[68]

9. SUMMARY and OUTLOOK

Diazirine reagents have immense utility in materials science. Multivalent small-molecule diazirines can be used for polymer crosslinking, photopatterning, and surface-functionalization of virtually any aliphatic material—including polymers like polyethylene, polypropylene, or poly(HNB) that have no functionality beyond C–C and C–H bonds. Functionalization of PDMS is also straightforward, opening new horizons in medical device manufacture. Additionally, poly(diazirine)s—polymers in which several diazirine units are present along the polymer chain—can be particularly useful as primers or adhesives,[52,63] or for the assembly of hydrogels.[69–71] In this context, a recent publication from the Hawker group,[72] in which diazirine-containing acrylate and methacrylate monomers were successfully polymerized using reversible addition–fragmentation chain transfer (RAFT) and atom-transfer radical polymerization (ATRP), is especially noteworthy. The availability of these and other polymeric diazirines will drive additional innovation in the future.

At the same time, it is critical to remember that not all diazirine reagents are created equal! Our findings strongly implicate electron-rich trifluoromethyl aryl diazirines as enabling greatly improved performance. These electronically optimized crosslinkers can be somewhat more challenging to synthesize (especially since the desired products have low activation temperatures) but the recent availability of ethylene-glycol conjugate **19** will help to mitigate this synthetic challenge. Compound **19** is available in only 2 synthetic steps from the TPD parent structure, and can be considered as a drop-in replacement for the more commonly used benzyl alcohol **16**—but with up to 10-fold improvement in C–H insertion efficacy. We hope that diazirine reagents derived from **19** (and electronically similar species) will be adopted more broadly across the field.

Of course diazirines are not the only reagents that can generate reactive intermediates capable of undergoing C–H insertion. Aryl azides (which afford nitrenes upon thermal or photochemical activation) and α-diazo esters (which produce carbenes adjacent to carbonyl groups) are somewhat faster to synthesize than diazirines, and both of these classes of reagents have been exploited in materials science.[73–76] The reactive intermediates generated from such reagents tend to be less well-behaved, however, than the carbenes derived from aryl diazirines. Aryl nitrenes undergo Buchner ring expansions unless the aromatic ring is extensively fluorinated, whilst carbenes positioned next to carbonyl groups can suffer unwanted Wolff rearrangements.[77] Electron-rich trifluoromethyl aryl diazirines are therefore generally preferred when one seeks controllable reactivity for the free carbene.[78]

Another reason for the preference of aryl diazirines over azides and diazoalkanes relates to ease of photo-activation (which governs photo-curing efficiency and photo-patterning speed). Aryl diazirines are activated at longer wavelengths than aryl azides, and generally have higher photo-activation efficiency than diazoalkanes.[28] However, most aryl diazirines have modest extinction coefficients, meaning that a high photon flux is required for photo-curing. Moreover, the range of wavelengths that can be used for photo-activation remains quite limited, notwithstanding the advent of reagents like **17** that can be activated with ~400 nm light. In parallel work, we recently found that diazirines can be conjugated to light-harvesting chromophores, allowing them to be activated with longer wavelengths of light. Two-photon activation can even be achieved, allowing high-intensity pulses of red light to be used.[79] This finding potentially opens the door to a broader set of diazirine-enabled reagents for both biological and materials science applications.

ASSOCIATED CONTENT

Supporting Information

Frequently asked questions for diazirine-based crosslinkers.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

Notes

The authors declare the following competing financial interest: J.W. is the cofounder of XLYNX Materials.

Biographies

Jeremy Wulff obtained his PhD at the University of Calgary, working under the supervision of Thomas Back. He undertook postdoctoral studies at Harvard University with Andrew Myers, before beginning his independent career at the University of Victoria in 2007. His research interests revolve around complex molecule synthesis, chemical biology, functionalized polymer synthesis, and—most recently—polymer crosslinking.

Mathieu Lepage obtained his *Diplôme d'ingénieur* and MSc in Organic Chemistry in 2011 at the University of Strasbourg. He received his PhD from the same university in 2014 (with Philippe Compain). He then took postdoctoral positions in Canada (with David Perrin at UBC and Jeremy Wulff at UVic) and the Netherlands (with Ben Feringa at the University of Groningen). He also worked in the industry for 2 years, in Groningen. His expertise encompasses the synthesis of small molecules, the radio-labeling of nuclear imaging agents, and the modification and crosslinking of polymers. In 2023, he started an independent research position as a CNRS researcher in Toulouse.

Stefania Musolino completed her PhD in Chemistry at the University of St Andrews under the supervision of James Taylor and Andrew Smith, and earned a MSc in Chemistry and Pharmaceutical Technologies from the University of Pisa. Following a MITACS postdoctoral fellowship with the Wulff group at the University of Victoria, she joined XLYNX Materials in 2022. Currently, she is the R&D manager at XLYNX, overseeing the design, testing, and production of innovative fluorine-free diazirine crosslinkers.

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