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Article

Decarboxylative Triazolation Enables Direct Construction of Triazoles from Carboxylic Acids

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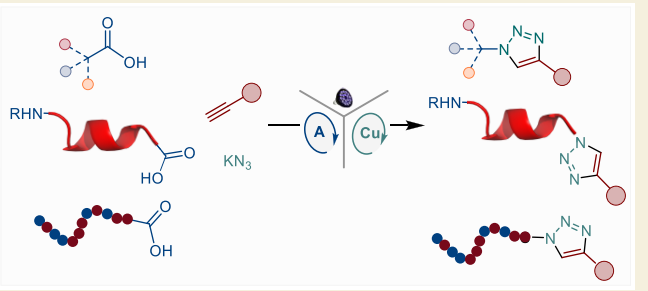
ABSTRACT: Triazoles have major roles in chemistry, medicine, and materials science, as centrally important heterocyclic motifs and bioisosteric replacements for amides, carboxylic acids, and other carbonyl groups, as well as some of the most widely used linkers in click chemistry. Yet, the chemical space and molecular diversity of triazoles remains limited by the accessibility of synthetically challenging organoazides, thereby requiring preinstallation of the azide precursors and restricting triazole applications. We report herein a photocatalytic, tricomponent decarboxylative triazolation reaction that for the first time enables direct conversion of carboxylic acids to triazoles in a single-step, triple catalytic coupling with alkynes and a simple azide reagent. Data-guided inquiry of the accessible chemical space of decarboxylative triazolation indicates that the transformation can improve access to the structural diversity and molecular complexity of triazoles. Experimental studies demonstrate a broad scope of the synthetic method that includes a variety of carboxylic acid, polymer, and peptide substrates. When performed in the absence of alkynes, the reaction can also be used to access organoazides, thereby obviating preactivation and specialized azide reagents and providing a two-pronged approach to C–N bond-forming decarboxylative functional group interconversions.



KEYWORDS: *carboxylic acids, radical reactions, triazoles, photocatalysis, visible light*

Development of new synthetic methodologies has a profound effect on organic synthesis, drug discovery, and materials science. In particular, new functional group interconversions can reveal previously inaccessible chemical space.[1−3] However, direct interconversions that provide access to the target functionality in one step and by means of simple catalytic processes remain underrepresented, and multiple steps involving protection, preactivation, and handling reactive intermediates, are typically required to achieve synthetic goals.[4,5]

Triazoles have recently emerged as some of the most synthetically important and versatile heterocycles. The structural similarity, rigidity, stability toward enzymatic cleavage, and the presence of both hydrogen bond donor and acceptor sites have rendered the triazole ring a key bioisosteric replacement for amides, carboxylic acids, and other carbonyl compounds.[6−10] Following the seminal studies by Huisgen,[11,12] the development of the copper-catalyzed azide alkyne cycloaddition (CuAAC) in the context of click chemistry[13−26] has facilitated access to triazoles and unraveled a plethora of applications as chemically robust linkers for bioconjugation, as well as in the areas of molecular recognition, catalysis, chemical sensing, polymer chemistry, and conducting materials (Figure 1).[27−36] Given the central role of organoazides in the cycloaddition reaction, the triazole-based click chemistry relies heavily on the availability of azides that can be challenging to prepare and handle and require additional synthetic manipulations to access, which limits the accessible chemical space of triazoles and impedes potential triazole-based click chemistry applications.[37]

A reaction that directly converts carboxylic acids to triazoles by a tricomponent coupling with alkynes and a simple azide source could obviate the isolation and handing of organoazides, enable previously unknown one-step bioisosteric replacement of carboxylic acid with triazoles, and dramatically increase the triazole accessible chemical space because of the substantial structural diversity and abundance of carboxylic acids in natural products, industrial feedstocks, biological macromolecules, and commodity polymers.

We hypothesized that such a tricomponent direct decarboxylative triazolation could be accomplished by a triple catalytic process that entails direct decarboxylative azidation and subsequent cycloaddition with alkynes. However, the combination of the two processes into one multicatalytic process is

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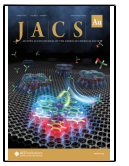

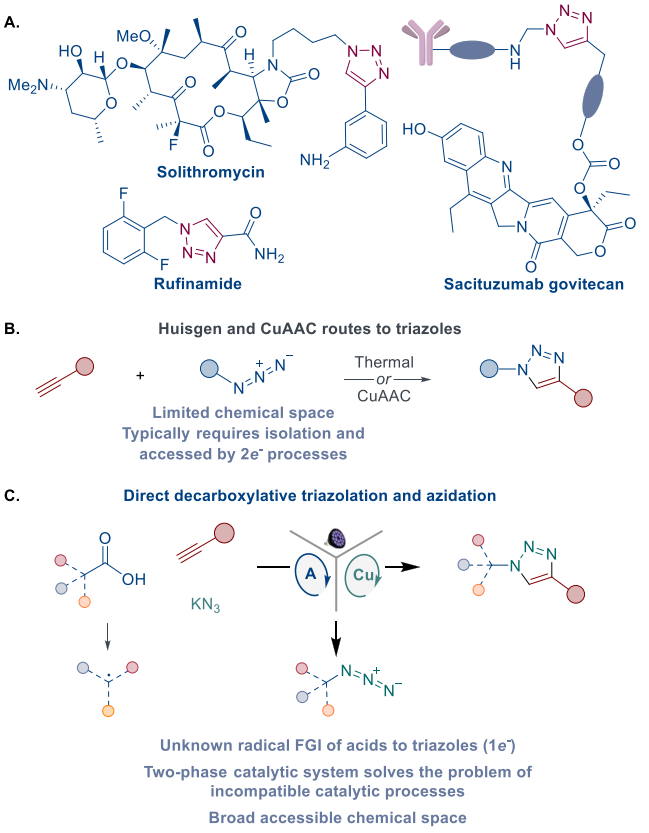

Figure 1. Triazoles and the direct decarboxylative triazolation. (A) Applications of triazoles. (B) Huisgen and CuAAC routes to triazoles. (C) Direct decarboxylative triazolation and azidation.

challenging because of the mismatch between the oxidatively mediated azidation and the oxidant-intolerant Cu^{I}-catalyzed cycloaddition that is instead diverted to a Glaser-type alkyne dimerization.[16−20] Additionally, an efficient photocatalytic system would be needed that can both facilitate direct decarboxylation of difficult-to-oxidize carboxylic acids to bypass the typically required preactivation to more reactive carboxylic acid derivatives[38−63] and also be compatible with the organoazide- and triazole-forming catalytic cycles. Importantly, the successful development of direct, tricomponent conversion of carboxylic acids to triazoles necessitates a broad-scope, direct decarboxylative azidation of carboxylic acids that is tolerant to oxidation-sensitive processes and is mediated by a simple inorganic azide source. Such a process remains unknown, as decarboxylative azidation has previously required preactivation of carboxylic acids and specialized azide reagents and has had a limited substrate scope, in particular with respect to carboxylic acids that do not bear stabilizing α-heteroatom substituents.[64−70] Furthermore, although photocatalytic decarboxylative *N*-alkylation has recently emerged as a new direction for the construction of N-heterocycles by C−N bond-forming reactions, the scope of heterocyclic products remains limited.[39,53]

We report herein the development of an unprecedented triple catalytic direct decarboxylative triazolation reaction that enables one-step conversion of a wide range of carboxylic acids to triazoles in a tricomponent coupling with alkynes and a simple and inexpensive azide source. The scope of the carboxylic acids includes small molecule, peptide, and polymer substrates, thereby pointing to applications that can take advantage of the abundance of the carboxylic group in biological and materials settings for the introduction of functional payloads. Importantly, the interrupted version of the reaction conducted in the absence of the alkyne produces organoazides directly from carboxylic acids and, for the first time without the need for specialized azide reagents, provides access to valuable synthetic intermediates and opening avenues for further functionalization.

RESULTS AND DISCUSSION

Analysis of the chemical space that is accessible by specific reactions and subsequent collation with the known product chemical space and the accessible chemical space of other reactions can provide important information about the synthetic potential of chemical methodologies and guide the development of new reactions.[71−73] The recently developed PARSE (Prospective Analysis of Reaction Scope) tool enables facile mapping of the accessible chemical space using molecular weight (MW), molecular complexity (C_m),[74] and fraction of sp^3 carbon atoms (Fsp^3)[75] as descriptors[76] and subsequent comparison between different reactions and with the total chemical space of expected reaction products.[56] Importantly, while the same chemical space can potentially be accessed by a sequence of several reactions, PARSE studies are limited to the comparison of direct transformations, which is in line with the main goal of such studies, that is, to inform and guide the development of more efficient synthetic methodologies for direct functional group interconversions.[58] Additionally, PARSE studies are intrinsically limited to the investigation of the product chemical space that can be accessed by direct transformations from the known reactant chemical space regardless of individual experimental conditions that are used to mediate the transformation. Given the focus on the underlying chemical transformation as a main design feature, PARSE does not provide information on the efficiencies of individual synthetic methods (i.e., specific sets of reaction conditions enabling the transformation), or outcomes of reactions with specific substrates. Instead, it informs about the characteristics of the product chemical space (e.g., geometric diversity and molecular complexity) that can be accessed by different direct transformations leading to a given product class, thereby enabling comparison of their accessible chemical space, as well as structural limitations, with regard to the types of accessible products. In this context, PARSE provides a quantitative, data-based analysis of reaction product chemical space that cannot be gleaned from simple comparison of relative sizes of reactant libraries or intuition and is an additional analytical tool in the growing set of quantitative cheminformatics approaches to reaction exploration.[71−73,77−80]

To gain insight into the potential synthetic impact of the direct decarboxylative triazolation on the accessible triazole chemical space, a PARSE study was first carried out wherein a data set of triazoles that are accessible from Pubchem-derived data sets of known carboxylic acids and alkynes was generated by means of a reaction SMARTS[81]-based protocol. The triazolation-accessible triazole chemical space was then compared with the chemical space of known triazoles and the chemical space of triazoles that are accessible by the cycloaddition of azides with alkynes as one of the most common methods of triazole construction (Figure 2). The PARSE study revealed a substantially more densely populated chemical space for the carboxylic acid-derived triazoles compared with the known triazoles (Figure 2A), especially in

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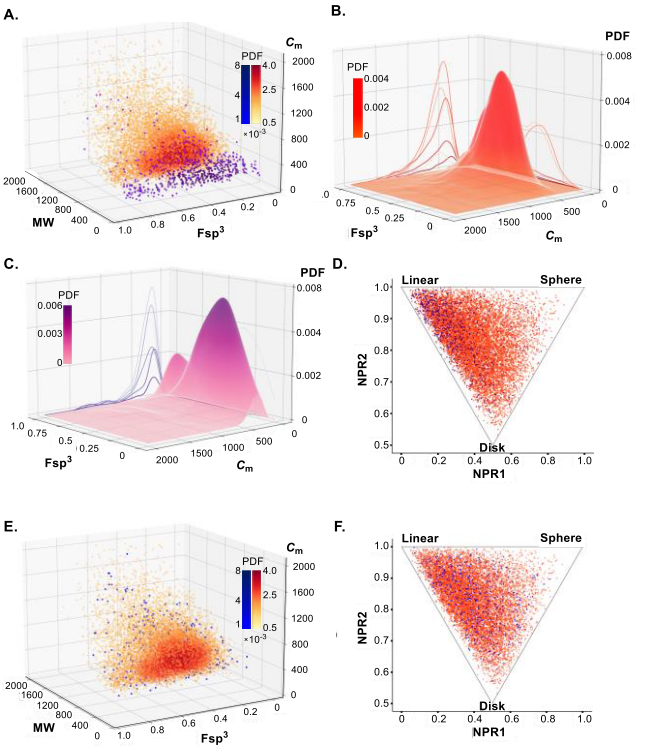

Figure 2. PARSE study of the accessible triazole chemical space of the direct decarboxylative triazolation of known carboxylic acids and alkynes (red/orange), known triazoles (purple), and the cycloaddition of known azides and alkynes (blue). Higher population density (PDF) is represented by darker colors. (A) The C_m/Fsp^3/MW plot for the direct decarboxylative triazolation of known carboxylic acids and alkynes (red/orange) and known triazoles (purple). (B) The population density plot for the decarboxylative triazolation-accessible triazoles. (C) The population density plot of known triazoles. (D) Geometric diversity population analysis for known (purple) and decarboxylative triazolation-accessible triazoles. (E) The C_m/Fsp^3/MW plot for the direct decarboxylative triazolation of known carboxylic acids and alkynes (red/orange) and the cycloaddition of known azides and alkynes (blue). (F) Geometric diversity population analysis for the azide-derived (blue) and decarboxylative triazolation-accessible triazoles.

the area of higher molecular complexity that describes structural and functional group content, and a broad representation across the Fsp^3 scale, which indicates that decarboxylative triazolation can provide access to complementary and more structurally complex triazole chemical space. This conclusion is supported by a comparison of the population density plots obtained by kernel density estimation (KDE) of the probability density function (PDF)[82] of the distribution of the triazolation-accessible (Figure 2B) and known triazoles (Figure 2C) in the Fsp^3/C_m chemical space that points to the greater density of structures in a higher molecular complexity region and broader distribution in the upper Fsp^3 region for the triazolation-accessible products (Figure 2B). Additionally, greater geometric diversity is also observed for the triazolation-accessible triazoles (Figure 2D), especially in the disk and sphere regions that are typically underrepresented in current drug discovery applications.[83] Similar trends are observed when the triazole chemical space that is accessible by the cycloaddition of azides and alkynes is compared with the chemical space of the triazolation-accessible triazoles (Figure 2D,E). Notably, triazolation provides access to a more densely populated chemical space because of a greater abundance of carboxylic acids. Taken together, the PARSE study indicates that direct decarboxylative triazolation can provide access to broad triazole chemical space, is complementary to current synthetic methods for triazole construction, and can facilitate construction of more structurally diverse libraries for drug discovery applications.

Following up on the results of the PARSE study, we next sought to identify the reaction conditions that enable decarboxylative triazolation (Figure 3). Experimental studies

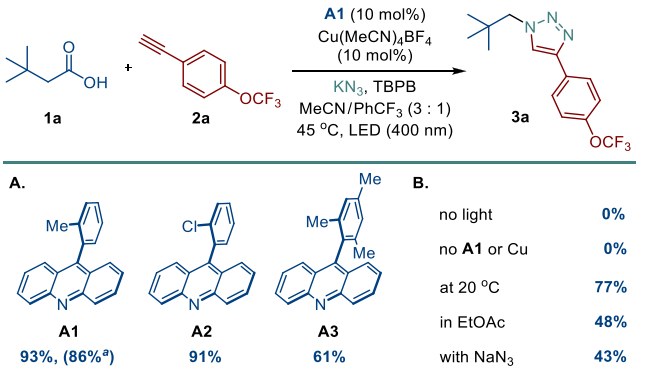

Figure 3. Direct decarboxylative triazolation. (A) Acridine photocatalysts. (B) Influence of other reaction parameters. Reaction conditions: alkyne **2a** (0.2 mmol), carboxylic acid **1a** (0.4 mmol), potassium azide (0.4 mmol), **A1** (10 mol %), *tert*-butyl perbenzoate (TBPB) (0.4 mmol), MeCN/PhCF$_3$ (3:1) (2 mL), LED (400 nm), 16 h. Yields were determined by ^{1}H NMR with 1,4-dimethoxybenzene as an internal standard. [a]Isolated yield.

revealed that carboxylic acid **1a** and alkyne **2a** can be converted to triazole **3a** in 93% yield (86% isolated yield) in a reaction with potassium azide catalyzed by acridine **A1** and a copper(I) salt in the presence of *tert*-butyl perbenzoate (TBPB) as an oxidant and 400 nm LED light in a mixture of acetonitrile and trifluorotoluene. Acridine **A1** emerged as an optimal photocatalyst, with *o*-chloro analogue **A2** providing similar levels of reaction efficiency, while more hindered acridine **A3** gave a lower yield of triazole **3a**. Notably, other photocatalysts (e.g., Ru and Ir complexes, eosin Y, and 4CzIPN) did not catalyze the reaction,[84] which underscores the versatility of the acridine photocatalytic system. Light and both acridine and copper catalysts were essential for the catalytic process. Furthermore, while warmer reaction conditions (e.g., 45 °C) had a beneficial effect on the reaction efficiency, the reaction at room temperature still delivered the product in a synthetically useful yield. By contrast, other solvents and azide sources resulted in a substantially lower reaction performance.

The scope of the reaction was evaluated next with a range of carboxylic acids and alkynes (Schemes 1 and S1). Primary aliphatic and benzylic carboxylic acids bearing ester, halogen, and unprotected phenol and indole groups were suitable substrates (**3b**−**3k**). Notably, *N*-methyltriazoles can be easily accessed from acetic acid by the tricomponent decarboxylative triazolation (**3k**) with acetic acid, thereby bypassing handling of the reactive and difficult to isolate methyl azide. Secondary carboxylic acids also produced the corresponding triazoles **3l**−**3v** in good yields. Both cyclic and acyclic secondary acids were equally reactive, and α-heteroatom-substituted as well as benzylic substrates were tolerated. Similarly, cyclic tertiary

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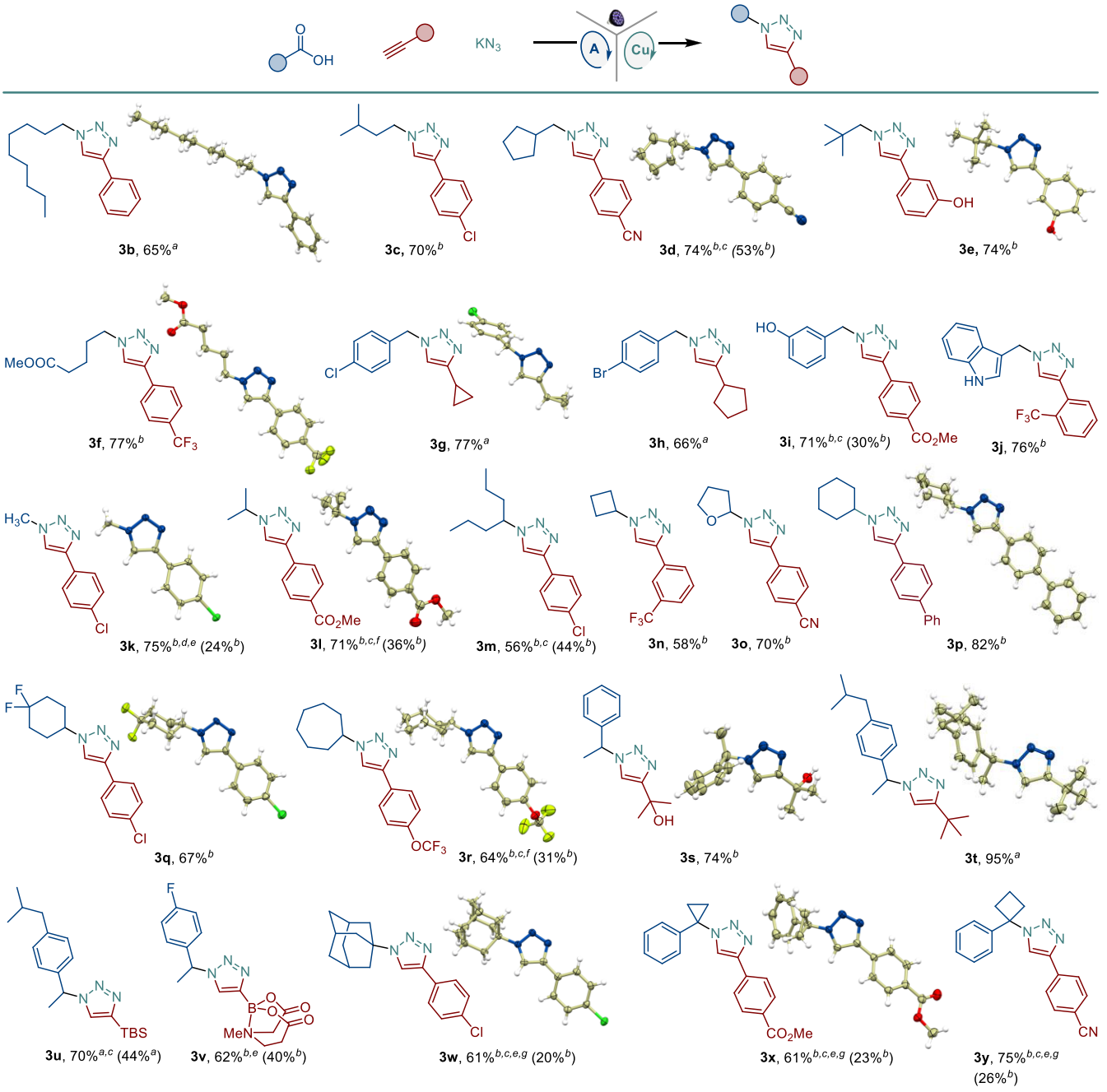
Scheme 1. Scope of Carboxylic Acids and Alkynes in the Direct Decarboxylative Triazolation



[a]Reaction conditions: alkyne (0.3−0.4 mmol), carboxylic acid (0.2 mmol), potassium azide (0.3 mmol), **A1** (10 mol %), $Cu(MeCN)_4BF_4$ (10−15 mol %), TBPB (0.24 mmol), $MeCN/PhCF_3$ (2−3:1, 1.8−3 mL), LED (400 nm), 45 °C, 16 h. [b]Alkyne (0.2 mmol), carboxylic acid (0.4 mmol), potassium azide (0.4 mmol), **A1** (10 mol %), $Cu(MeCN)_4BF_4$ (10−15 mol %), TBPB (0.4 mmol), $MeCN/PhCF_3$ (2−3:1, 1.8−3 mL), LED (400 nm), 45 °C, 16 h. [c]With dtbpy (10−15 mol %). [d]With bpy (15 mol %). [e]Acetone (2 mL) as a solvent. [f]$MeCN/PhCF_3/H_2O$ (2:1:1, 2 mL) as a solvent. [g]With **A3** (10 mol %) as a photocatalyst.

acids, including those featuring strained small rings were efficiently converted to triazoles (e.g., **3w**−**3y**), while acyclic tertiary acids were unsuitable for the triazolation. The reaction also tolerated a broad array of alkynes. Aromatic alkynes featuring halogen, cyano, hydroxy, ester, and the medicinally relevant trifluoromethyl and trifluoromethoxy groups all produced the corresponding triazoles (**3b**−**3f**, **3i**−**3r**, **3w**−**3y**). Aliphatic alkynes were also suitable coupling partners (**3g**, **3h**, **3s**−**3v**). Importantly, the reaction can also be extended to alkynes bearing silyl and boryl groups, which affords facile access to triazoles **3u** and **3v** that may be used for subsequent functionalizations.[85−87]

The synthetic scope and functional group tolerance of the reaction were further examined with an array of natural products and active pharmaceutical ingredients (Scheme 2). The reaction enabled a smooth conversion of a number of nonsteroidal anti-inflammatory drugs and (hetero)aromatic and aliphatic alkynes to the corresponding triazoles, featuring pyridyl, boryl, and unprotected carbazole and hydroxy groups, as well as indole (**4a**−**4q**). Notably, *cis*-pinonic acid underwent

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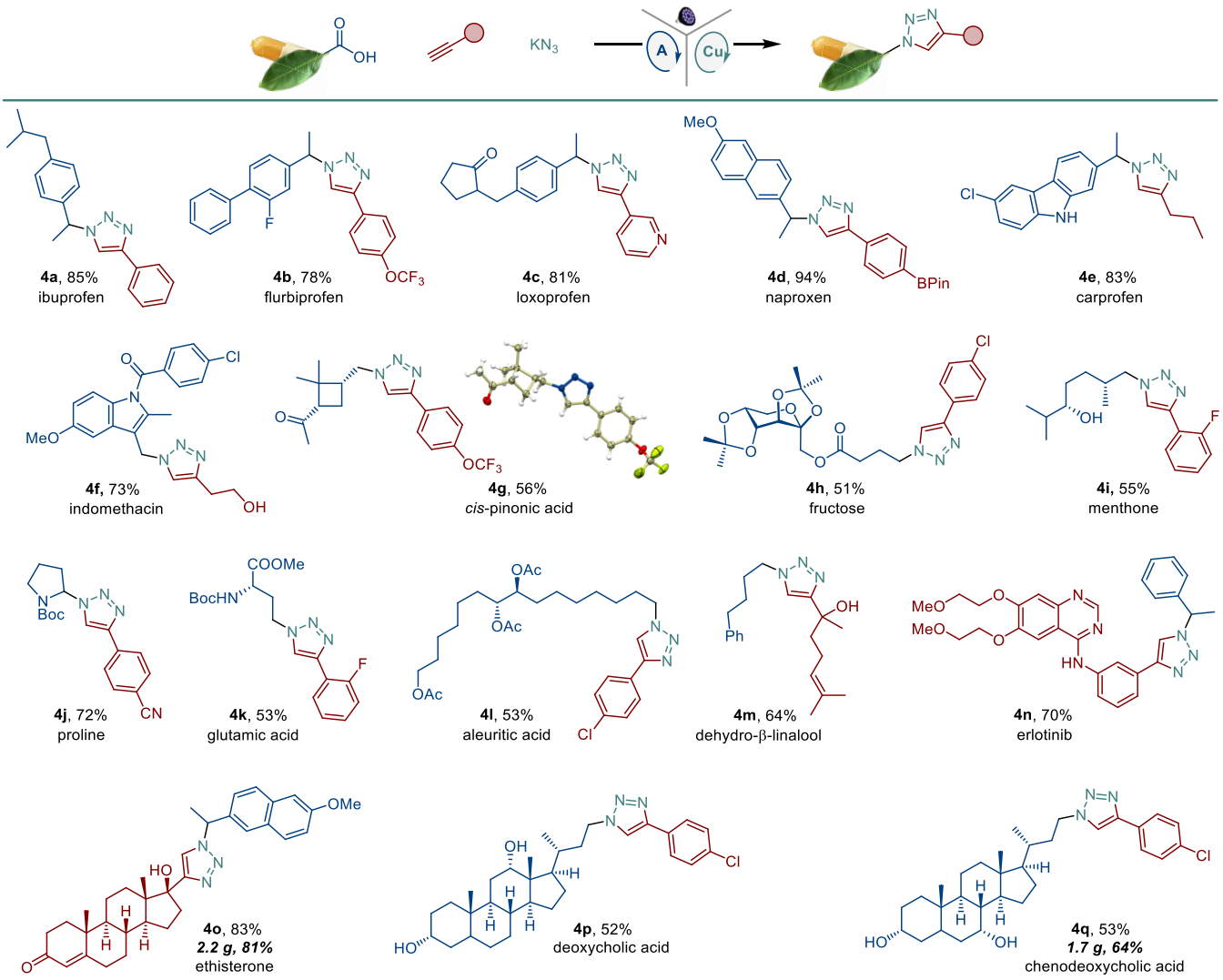
Scheme 2. Functionalization of Natural Products and Drugs by Direct Decarboxylative Triazolation



[a]Reaction conditions: alkyne (0.3−0.4 mmol), carboxylic acid (0.2 mmol), potassium azide (0.3 mmol), **A1** (10 mol %), $Cu(MeCN)_4BF_4$ (10−15 mol %), TBPB (0.24 mmol), $MeCN/PhCF_3$ (2−3:1, 1.8−3 mL), LED (400 nm), 45 °C, 16 h. [b]Alkyne (0.2 mmol), carboxylic acid (0.4 mmol), potassium azide (0.4 mmol), **A1** (10 mol %), $Cu(MeCN)_4BF_4$ (10−15 mol %), TBPB (0.4 mmol), $MeCN/PhCF_3$ (2−3:1, 1.8−3 mL), LED (400 nm), 45 °C, 16 h. [c]With dtbpy (10−15 mol %). [d]With bpy (15 mol %). [e]$MeCN/PhCF_3/H_2O$ (2:1:1, 2 mL) as a solvent. [f]With **A3** (10 mol %) as a photocatalyst. [g]1.1:1 dr. [h]80% yield on a 1.5 mmol scale.

a clean conversion to triazole **4g** without the previously documented concomitant ring-opening of the intermediate alkyl radical,[52] thereby pointing to a rapid radical capture. Derivatives of fructose and menthone also readily produced triazoles **4h** and **4i**. Amino acids can also be used as substrates to produce triazole analogues of proline and glutamic acid **4j** and **4k**. Similarly, aleuritic acid afforded triazole **4l**. Alkynyl-group-containing substrates can also be converted to triazole analogues, as shown for dehydro-*β*-linalool (**4m**), the anticancer drug erlotinib (**4n**), and the progestin drug ethisterone (**4o**), thereby demonstrating functional group tolerance of the reactive enone and diarylamine groups that may also undergo decarboxylative *N*-alkylation and alkyl addition reactions. Likewise, the unprotected bile acids readily produced triazoles **4p** and **4q**. Importantly, the reaction can be carried out with either acid or alkyne as a limiting reagent and used to access triazoles on the gram scale (**4o** and **4q**). The addition of nitrogenous ligands (e.g., bpy and dtbpy) also improved the reaction performance for some less reactive substrates (**3d, 3i, 3k−3m, 3r, 3u, 3w−3y, 4h, 4i, 4n−4q, 5a−5e**). Acetone also proved to be an optimal solvent for acetic acid (**3k**) and tertiary carboxylic acids (e.g., **3w−y**), while 9-mesitylacridine (**A3**) was the catalyst of choice for triazole **A3**. These results indicate that further improvements of the reaction efficiency can be achieved for specific substrates by adjusting key reaction parameters, for example, the ligand, solvent, and photocatalyst.

The azide−alkyne cycloaddition-based click chemistry has emerged as an important tool in biorthogonal chemistry and for grafting applications in materials science that require preinstallation of the azide or alkyne group in the biomolecule or polymeric material of interest.[27] We hypothesized that the new decarboxylative triazolation reaction could enable direct introduction of alkyne-tethered probes by taking advantage of unprotected carboxylic acid groups that are present in peptides and polymers. Indeed, decarboxylative triazolation was readily

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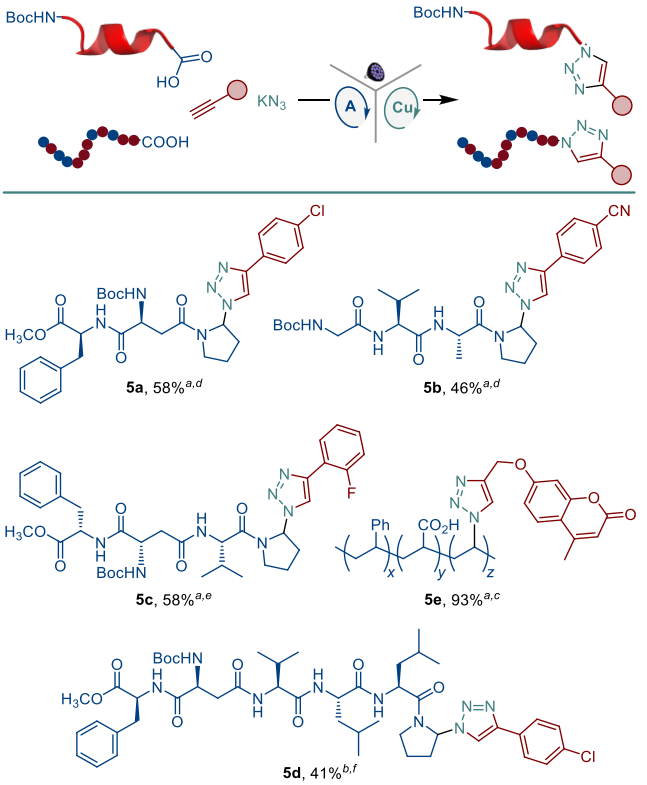
accomplished with a range of tri-, tetra-, and pentapeptides bearing a terminal proline residue (**5a**–**5d**), thereby indicating that the reaction can be used for click-decarboxylative coupling with alkynes (Scheme 3). Similarly, a fluorescent coumarin

Scheme 3. Direct Decarboxylative Triazolation of Peptide and Polymer Substrates



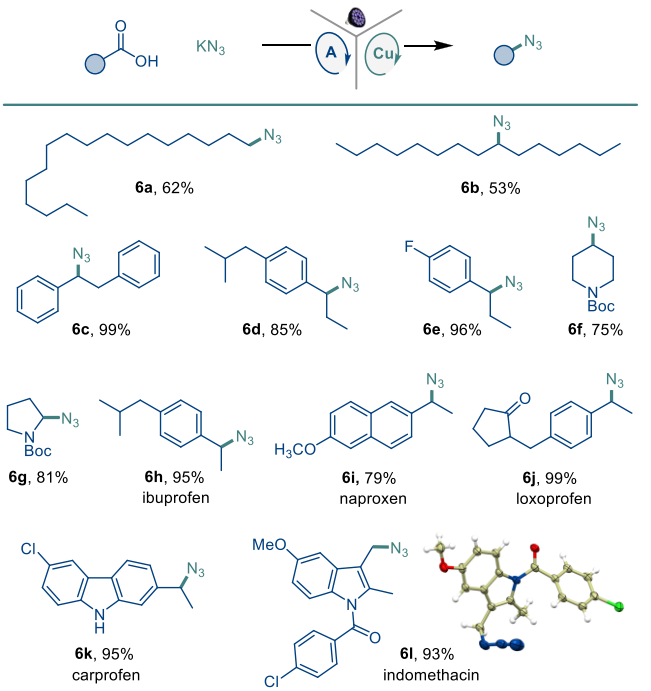
[a]Reaction conditions: alkyne (0.3–0.4 mmol), carboxylic acid (0.2 mmol), potassium azide (0.3 mmol), **A1** (10 mol %), $Cu(MeCN)_4BF_4$ (10–15 mol %), TBPB (0.24 mmol), $MeCN/PhCF_3$ (2–3:1, 1.8–3 mL), LED (400 nm), 45 °C, 16 h. [b]Alkyne (0.2 mmol), carboxylic acid (0.4 mmol), potassium azide (0.4 mmol), **A1** (10 mol %), $Cu(MeCN)_4BF_4$ (10–15 mol %), TBPB (0.4 mmol), $MeCN/PhCF_3$ (2–3:1, 1.8–3 mL), LED (400 nm), 45 °C, 16 h. [c]30.4% triazole content. [d]1.1:1 dr. [e]1.2:1 dr. [f]1:1 dr.

probe was successfully grafted on a styrene–acrylic acid copolymer (**5e**), which points to potential applications in polymer upcycling and development of new advanced materials.[88]

To test if azides are formed as intermediates in the decarboxylative triazolation, the reaction was carried out in the absence of the alkyne coupling partner (Scheme 4). A range of azides were produced, which points to azides as reactive intermediates. Acyclic and cyclic aliphatic and benzylic acids were readily converted to the corresponding azides (**6a**–**6l**), including those derived from active pharmaceutical ingredients (**6h**–**6l**), thereby indicating that the reaction affords access to versatile azide analogues that can be used for further structural diversification.

Experimental and computational studies were carried out to further clarify the mechanism of the reaction. Experiments with TEMPO in a reaction of acid **7** and alkyne **8** suppressed formation of triazole **9**, which confirmed the intermediacy of alkyl radicals in decarboxylative triazolation (Figure 4A).

Scheme 4. Direct Decarboxylative Azidation[a]



[a]Reaction conditions: carboxylic acid (0.2 mmol), **A2** (10 mol %), $Cu(MeCN)_4BF_4$ or $Cu(hfac)_2$ (10 mol %), KN_3 (0.3 mmol), TBPB (0.24 mmol), $MeCN/PhCF_3$ (3:1), LED (400 nm), 25–27 °C, 16–24 h.

Furthermore, kinetic measurements pointed to a significant accumulation of azide intermediate **10** prior to the formation of triazole product **9**, which suggests that the organoazide–alkyne cycloaddition is inhibited in the early stages of the triazolation process (Figure 4B) and points to the prevalence of the Cu^{II} species that is an intermediate in the oxidatively mediated azidation catalysis (vide infra) but is not catalytically active in the azide alkyne cycloaddition.[16−19,37]

The two-phase decarboxylative azidation/cycloaddition process is consistent with the experiments that ruled out an alternative pathway, that is, formation of a 1*H*-triazole intermediate with subsequent decarboxylative *N*-alkylation (Figure 4C). 1*H*-Triazole **11** was not detected in the reaction mixture under the standard reaction conditions, as the aprotic medium suppresses the formation of hydrazoic acid because of the low acidity of carboxylic acids in such solvent systems (cf., pK_a = 7.9 for HN_3 and 12.3 for AcOH).[89] Indeed, formation of 1*H*-triazole typically requires a polar aqueous medium and temperatures >100 °C.[90,91] In line with this conclusion, no hydrazoic acid was detected in the reactor headspace under the reaction conditions of decarboxylative triazolation. Furthermore, a decarboxylative *N*-alkylation of triazole **11** proceeded with a very low yield under the triazolation reaction conditions and produced a mixture of *N*-alkyl regioisomers (Figure 4C).

Computational studies were further carried out to clarify the mechanistic roles of an inner sphere radical addition/reductive elimination pathway and an outer sphere radical polar crossover mechanism that involves a carbocation intermediate formed by single-electron transfer from the alkyl radical to Cu^{II} (Figure 4D). Given the differences between the oxidation potentials of aliphatic and benzylic radicals, calculations were conducted for both types of systems. Following an exergonic

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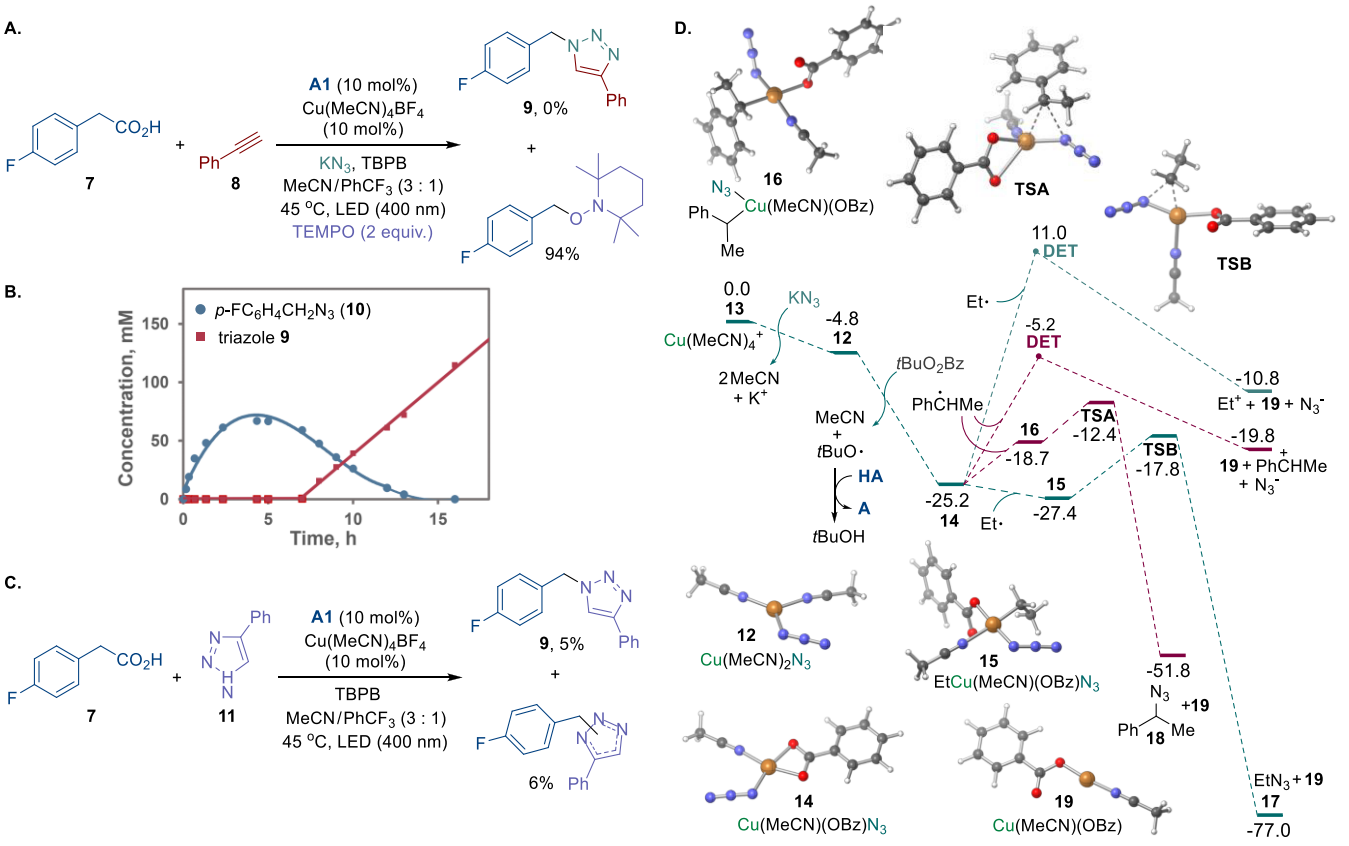

Figure 4. Kinetic and computational studies of direct decarboxylative triazolation. (A) Radical trapping experiments with TEMPO. (B) Kinetic profile of the decarboxylative triazolation reaction of acid **7** and alkyne **8**. (C) Decarboxylative coupling with triazole **11**. (D) Computed Gibbs free energy profile of the decarboxylative azidation process (ΔG, kcal/mol).

formation of Cu^{I} intermediate **12** from precursor **13**,[92] oxidation with TBPB produces Cu^{II} species **14** along with *tert*-butoxy radical that regenerates the acridine photocatalyst from acridinyl radical **HA** (Figure 5). Subsequent barrierless capture of the alkyl radical by Cu^{II} intermediate **14** was exergonic for the ethyl radical (**15**) but endergonic for a secondary benzylic radical (**16**). Conversely, the reductive elimination occurred over a lower barrier from benzylic intermediate **16** (**TSA**, $\Delta G^{\ddagger}$ = 6.3 kcal/mol), while the barrier was somewhat higher but also readily accessible for ethyl intermediate **15** ($\Delta G^{\ddagger}$ = 9.6 kcal/mol), which resulted in a highly exergonic formation of alkyl azide products **17** and **18** and Cu^{I} species **19**. By contrast, the dissociative single electron transfer (DET) pathways proceeded with prohibitively high barriers (e.g., $\Delta G^{\ddagger}$ = 36.2 kcal/mol for ethyl and 20.0 kcal/mol for 1-phenylethyl radical) and resulted in an exergonic generation of the corresponding carbocations, thereby pointing to the kinetically more favorable radical inner sphere pathway for the azide formation.

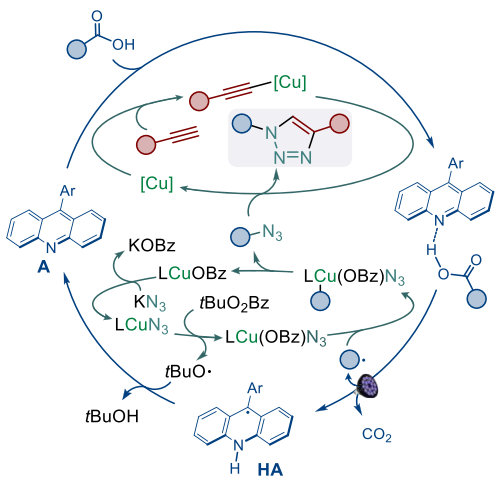

Figure 5. Catalytic system for the direct decarboxylative triazolation.

Taken together, the experimental and computational studies indicate that the acridine-photocatalyzed decarboxylative triazolation generates an alkyl radical that is subsequently converted to the organoazide intermediate by a radical copper-catalyzed pathway (Figure 5), thereby resulting in the regeneration of the acridine photocatalyst via a hydrogen transfer by *tert*-butoxy radical. The ensuing uptake of the intermediate organoazide into the third catalytic cycle in a reaction with copper acetylide[15−17] (e.g., generated in a reaction of basic benzoate **19** with the alkyne[93]) results in the formation of the triazole product.

CONCLUSION

In conclusion, we have developed a decarboxylative triazolation reaction that enables a previously inaccessible direct conversion of carboxylic acids to triazoles by a tricomponent coupling with alkynes and a simple azide reagent. The scope of the reaction encompasses a wide range of alkynes and carboxylic acids, including polymer and peptide

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substrates, while a data-driven inquiry of the triazolation-accessible chemical space suggests that further development of the direct transformation may lead to an expansion of the structural diversity and molecular complexity of the accessible triazole chemical space. Mechanistic studies point to a triple catalytic process that entails an acridine photocatalysis-driven decarboxylative radical generation, followed by a sequence of two mutually incompatible copper catalytic cycles, that is, an oxidatively mediated azidation and an oxidant-intolerant cycloaddition whose merger is facilitated by a two-phase process. The reaction can be readily adapted for the construction of versatile yet synthetically challenging organo-azides without the need for preactivation and specialized azide reagents, thereby opening new directions to further development of multicatalytic functional group interconversions of carboxylic acids.

METHODS

General Procedure for the Direct Decarboxylate Triazolation

Potassium azide (0.3 mmol) was added to a solution of carboxylic acid (0.2 mmol), the acridine photocatalyst (0.02 mmol, 10 mol %), $Cu(MeCN)_4BF_4$ (0.02 mmol, 10 mol %), alkyne (0.3−0.5 mmol), and *tert*-butyl peroxybenzoate (78 mg, 0.24 mmol) in acetonitrile/trifluorotoluene (3:1 v/v, 1.8−3 mL) (0.3 mmol) in an 8 mL test tube equipped with a stir bar. The reaction mixture was degassed by briefly passing argon on the solution surface. The test tube was capped, and the reaction mixture was irradiated with LED light (λ = 400 nm) while stirring at 45 °C for 16−36 h. The reaction mixture was then cooled to rt, and a saturated solution of EDTA disodium salt adjusted to pH 7.5 with sodium hydroxide (1.5 mL) was added, followed by ethyl acetate (10 mL). After extraction with ethyl acetate (3 × 10 mL), the organic phases were combined, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the remaining material was purified by column chromatography on silica gel to give the triazole product.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.2c00606.

Experimental and spectral details for all new compounds and all reactions reported (PDF)

X-ray crystallographic details for **3a**, **3b**, **3d−g**, **3k**, **3l**, **3p−t**, **3w**, **3x**, **4g**, **6l**, **S2**, **S5**, **S6**, **S9** (ZIP)

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Notes

The authors declare no competing financial interest.

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