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Site-selective conversion of azido groups at carbonyl α-positions into oxime groups leading triazide to a triple click conjugation scaffold†

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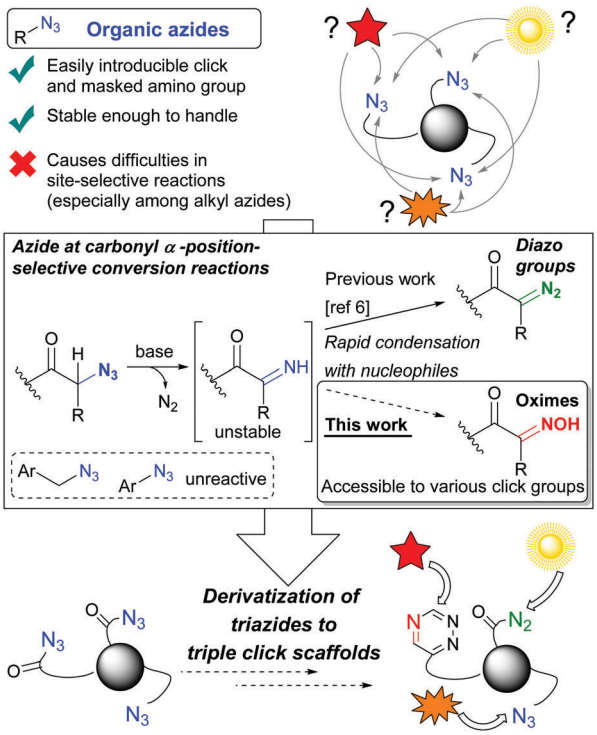
This paper reports the selective conversion of alkyl azido groups at the carbonyl α-position into oximes through β-elimination of dinitrogen, followed by transoximation. With this method and diazo conversion, a triazido molecule was transformed into a triple click conjugation scaffold allowing one-pot four-component coupling.

Element-block materials into which a variety of functional units can be incorporated have been investigated for application to advanced imaging probes and high-performance polymers.[1] For this purpose, strategies integrating multiple functional molecules into one compound must be further explored. Organic azides (R-N_3) have received much attention in click chemistry for establishing robust conjugation between two molecules as well as for the synthesis of versatile and valuable bioactive and optical compounds.[2,3] Click one-on-one conjugation using mono-azido substrates has been well utilized in a broad range of scientific area, including chemical biology and polymer synthesis. However, with multiple azido compounds (multi-azides) such as triazides, site-selective conjugation remains difficult, especially among alkyl azido moieties, because of their similar reactivities (Scheme 1).

To date, site-selective multicomponent conjugation strategies have been developed using platform compounds possessing various types of click functionalities such as aldehydes for oxime ligation, and olefins for thiol–ene reactions, *via* one-pot sequential click integration of multiple components.[4] Although azides may also be used in this regard, the number of azido groups is limited to one in most cases. Owing to the synthetic accessibility of the substrates and the high reactivity with sufficient molecular stability, multi-azides have sparked interest in the site- or chemo-selective manipulation of azido groups at specific positions, including conjugation of molecules with scaffold compounds possessing multiple clickable groups for versatile functionalization.[5]



Scheme 1 Site-selective manipulation of triazides toward triple click aza scaffolds.

We recently reported the site-selective conversion of alkyl azides at carbonyl α-positions to diazo click groups, with retention of the aryl and unfunctionalized alkyl azide moiety, which was extended to successive site-selective conjugations using triazides.[6] This reaction proceeds through β-elimination of dinitrogen from the azido groups to yield unstable imino carbonyl intermediates,[7] followed by rapid condensation with sulfonyl hydrazide/decomposition of sulfonyl hydrazones. For site-selective manipulation of multi-azides to other click functions with different reactivity, the nucleophiles on the iminocarbonyl intermediates can be altered to provide various click functions

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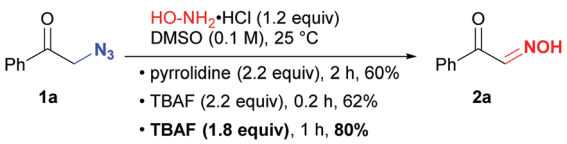
to the molecules. For this purpose, we focused on oximes that can be obtained from imines with hydroxylamines. These are known as clickable groups and are also precursors of a series of other click functions such as nitrones and nitrile oxides.[8,9] This new site-selective conversion, in combination with our previous diazo synthesis, can transform easily accessible but indistinguishable triazido compounds into distinguishable triple click scaffolds. We herein report a method that allows selective transformation of the azido group at the carbonyl α-position into an oxime group. With this method and with diazo conversion, a tris(alkylazido) molecule with indistinguishable azido groups was delivered to a triple click conjugation aza scaffold that achieved site-selective integration of four components in one pot.

Although a similar reaction system was established in our previous work on diazo synthesis,[6] we commenced our synthesis by optimization of the reaction conditions for oxime conversion (Scheme 2). With ketone **1a** pyrrolidine and tosyl hydrazide successfully delivered diazo products in good yield. However, oxime synthesis using pyrrolidine and hydroxylamine salt afforded the desired aldoxime **2a** in only 60% yield. Upon changing the base to tetrabutylammonium fluoride (TBAF),[6,10] **2a** was obtained in a similar yield but in a shorter time. After investigation, 1.8 equiv. of TBAF was effective for the reaction to obtain **2a** in 80% yield. Use of a hydroxide reagent (TBAOH) gave **2a** only in 26% yield.

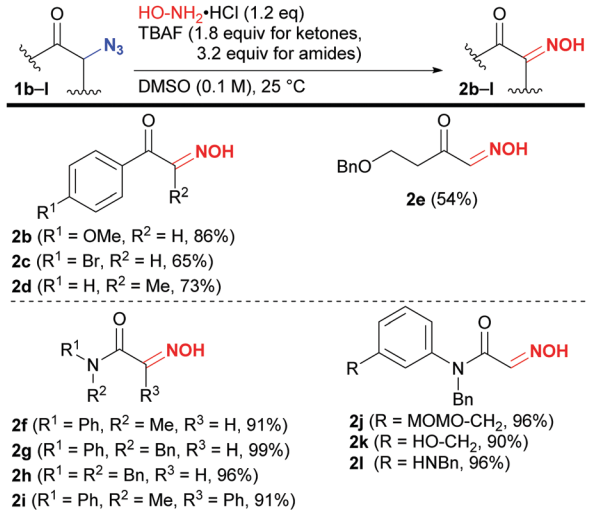
After optimizing the reaction conditions for oximes, we examined the scope of mono-azides to demonstrate the generality of this method (Scheme 3). *para*-Substituted analogs of α-azido acetophenones **1b,c** were efficiently transformed into **2b,c** in 86% and 65% yields, respectively. The secondary alkyl azido ketone **1d** could produce ketoxime **2d** in 73% yield. Dialkyl ketone **1e** was successfully transformed into α-oxime ketone **2e** in 54% yield, without potential β-elimination of the benzyloxy group.

Next, we studied the reaction with amides. Although 1.8 equiv. of TBAF was not sufficient to convert the starting amido azides, increasing the amount of TBAF to 3.2 equiv. afforded aldoximes and ketoxime **2f–i** in above 90% yields. In the case of previous diazo conversion reactions, protection of the hydroxyl group was necessary to obtain products in high yields.[6] On the other hand, this oxime conversion aided the efficient transformation of starting substrates **1j–l** possessing protected and unprotected alcohols as well as amino groups into **2j–l** in 96%, 90%, and 96% yields, respectively.

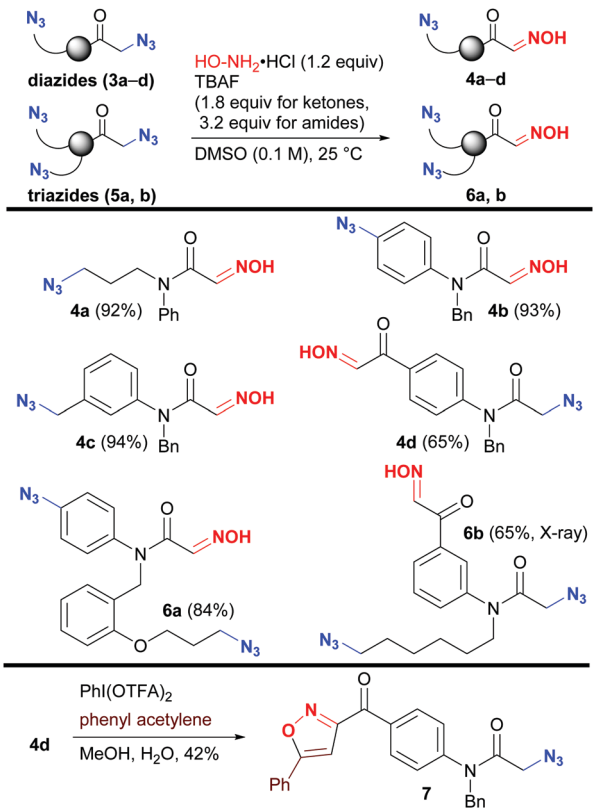
With the successful results from mono-azides in hand, we attempted to expand the scope of the substrates to di- and triazides for site-specific conversion (Scheme 4). All azido groups in the substrates were introduced in one step, which demonstrated their easy accessibility, as reported previously.[6] Diazides of α-azido amides with alkyl and aryl azido moieties **3a,b** were successfully transformed into azido oximes **4a,b** in 92% and 93% yields, respectively. The potentially reactive benzylic azide in **3c** was tolerated under the reaction conditions to give **4c** in 94%. Equivalent control of TBAF could selectively transform the azide at the α-keto moiety into oxime **4d** in the presence of α-azido amide. Subsequently, we focused on triazides. Selective manipulation of the azide at the α-carbonyl position in **5a** with aryl and unsubstituted



Scheme 2 Optimization of base conditions for oxime synthesis from azide **1a**.



Scheme 3 Scope of mono-azido substrates.

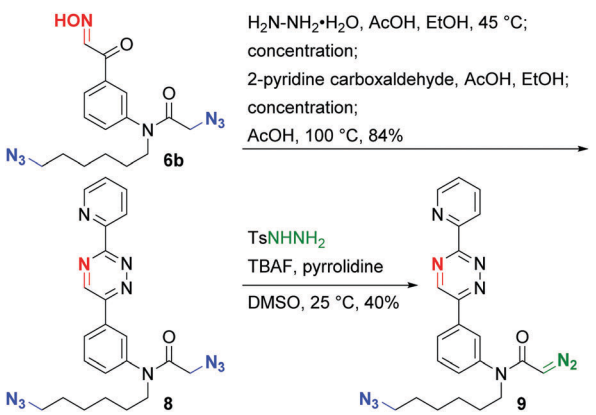


Scheme 4 Scope of di- and triazido substrates and chemoselective reaction.

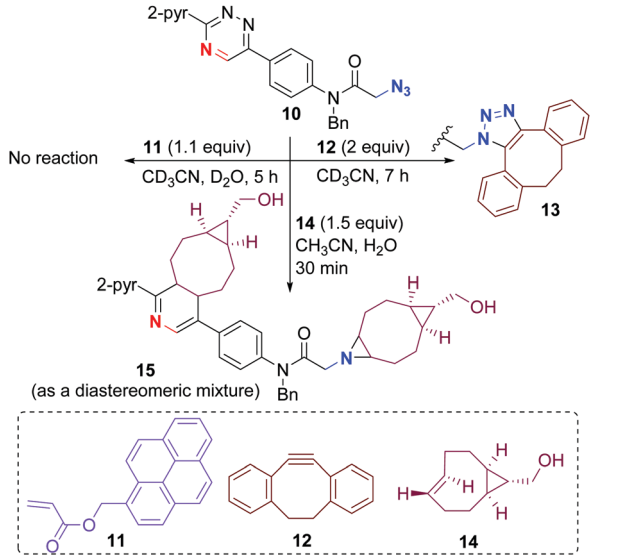
alkyl azido moieties was achieved and diazido α-hydroxyimino ketone **6a**, which possessed distinguishable aryl and alkyl azido groups,[3e,4e] was furnished in 84% yield. Tris(alkyl azido) compound **5b** containing keto- and amido-azido fragments was also position-selectively converted at the ketone site to afford **6b**. The versatile utility of the obtained azido oximes in chemoselective conjugation was demonstrated by [3 + 2] cycloaddition through oxidation of the oxime moiety in **4d** to nitrile oxide,[9] which gave isoxazole **7** in the presence of the azido group.[11]

Although the oxime group is known to be a conjugation functional group,[8] our next approach was to deliver the prepared oximes to reactive but bench-stable click groups. For this purpose, α-hydroxyimino carbonyl structures, which are accessible by our method, are suitable because they are synthetic precursors of disubstituted 1,2,4-triazines, which are selectively clickable with *trans*-cyclooctenes.[12] Thus, combination of this oxime conversion with our previous diazo conversion[6] could give reagent-free triple conjugation scaffold compounds[4] possessing three different clickable aza functions from tris(alkylazido) materials in which position discrimination by typical click reactions is difficult. Diazido α-hydroxyimino ketone **6b**, obtained from **5b** by ketone-selective conversion (Scheme 4), was subjected to a one-pot sequence involving two hydrazonation reactions and subsequent cyclization to obtain 1,2,4-triazine **8** (Scheme 5).[12c] After diazo conversion of the azide at the amide α-position,[6] triple click candidate **9** with three different aza functions was successfully obtained.

Prior to the triple click conjugation using **9**, we tested the chemoselectivity of the coupling partners. Although the selectivity of acrylates and strained alkynes in reactions with azido and diazo compounds was demonstrated previously,[13,14] the selectivity of our substrates in the presence of 1,2,4-triazines or *trans*-cyclooctenes should be experimentally clarified (Scheme 6). With azido triazine **10** prepared from **4d** (see the ESI†), we confirmed that both triazine and the alkyl azide moiety were tolerated in the presence of acrylate **11** which was for conjugation with a diazo moiety.[6,14] With dibenzocyclooctyne **12**,[3e] the alkyl azido moiety immediately underwent [3 + 2] cycloaddition, while the 1,2,4-triazine moiety did not undergo cycloaddition. On the other hand, cyclopropane-fused *trans*-cyclooctene **14**[15] attached not only to triazine,[12] but also to the alkyl azide rapidly within 30 min to give overreaction adduct **15**

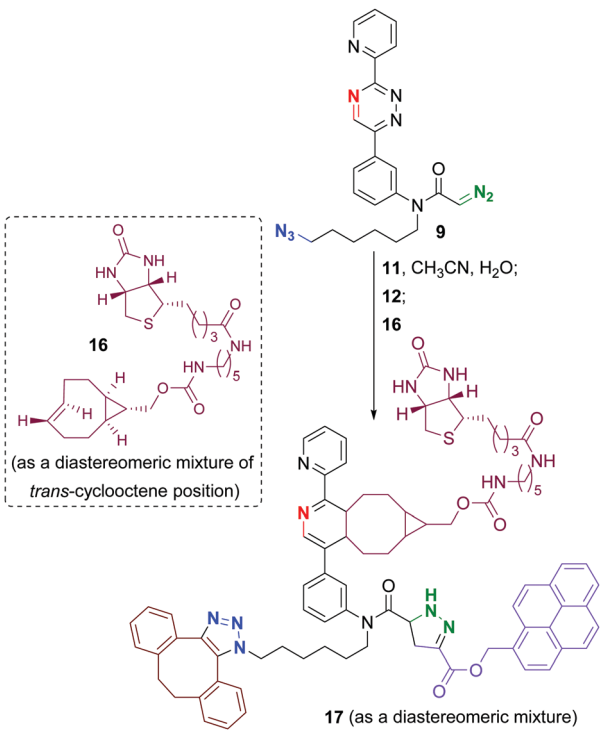


Scheme 5 Transformation to a triple click scaffold candidate.



Scheme 6 Model study on chemoselectivity between 1,2,4-triazine and azide.

conjugated through dihydropyridine and aziridine by [3 + 2] cycloaddition/loss of dinitrogen,[16] without chemoselectivity. The reaction with monoazide **1g** and **14** (1.1 equiv.) also demonstrated rapid coupling within 40 min, although cycloaddition of **14** with alkyl azides is much slower than that with 1,2,4-triazines.[17] This selectivity could be improved by use of less reactive dioxolane-fused *trans*-cyclooctene.[12c,18] Nonetheless, these results suggest the appropriate conjugation order of partners to **9**: (1) diazo with



Scheme 7 One-pot reagent-free sequential triple click conjugation using an aza scaffold.

acrylate; (2) azide with cyclooctyne; and then (3) triazine with cyclopropane-fused *trans*-cyclooctene.

Having established the model study, we conducted a four-component coupling reaction with **9** by sequential one-pot triple click conjugation (Scheme 7). Pleasingly, we obtained the conjugated product **17** in 44% yield (76% per conjugation step) by the successive addition of pyrene-connected acrylate **11**, cyclooctyne **12**, and *trans*-cyclooctene **16** linked with biotin to the solution of **9**. All the components were selectively introduced, leading to the desired product by appropriate order of conjugation without any coupling reagents.

In summary, we have achieved the site-selective conversion of azido groups at carbonyl α-positions to oxime groups in one step. As this transformation is dependent on the high reactivity at the carbonyl α-positions, aryl and unreactive alkyl azides were excluded. By combining this method with the previously developed diazo conversion, a tris(alkylazido) compound, which is difficult to discriminate by click conjugation, could be successfully transformed into an azido diazo triazine molecule; in other words, sequential one-pot triple click conjugation was achieved in a chemoselective fashion. The developed selective azido-manipulation method may further expand the efficiency of organic azides and aid site-selective assembly of multiple functional components onto a single molecular scaffold, thus facilitating the development of functional materials and biochemical tools.

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Conflicts of interest

There are no conflicts to declare.

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