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Taming the reactivity of alkyl azides by intramolecular hydrogen bonding: site-selective conjugation of unhindered diazides†

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Organic azides are still in the center of click chemistry connecting two molecules. However, taming the conjugation selectivity of azides is difficult without the help of bulky groups. We report herein the unique reactivities of α-azido secondary acetamides (α-AzSAs) as minimal and unhindered azide structures. The NH–azide interaction in the α-AzSAs, supposed by DFT calculations, allowed selective conjugation in the presence of other azido moieties, even without steric hindrance. With Staudinger–Bertozzi ligation, α-AzSAs underwent conjugation prior to the other primary alkyl azides. On the other hand, in propargyl cation-mediated triazole synthesis, other alkyl azides, including tertiary alkyl azides, underwent the conjugation faster than α-AzSAs. We also demonstrated site-selective integration of the functional components onto the diazide modular hubs.

Introduction

In a broad range of scientific areas, including chemical biology and polymer synthesis,[1,2] click chemistry[3] represented by organic azides[4] has received much attention, and it involves conjugation of two molecules concisely. Beyond this established one-on-one conjugation,[5] a multi-click modular hub strategy can integrate multiple compounds onto one scaffold molecule (Fig. 1).[6] Owing to the high reactivity with sufficient stability and small steric influence, multi-azides, compounds possessing multiple azido groups, have sparked interest in click scaffolds of multicomponent integration. In addition, multi-azides are easily accessible multi-click substrates, for example, by late-stage global azidation and polymerization of monoazides.[7,8] For these reasons, multi-azides could serve as so-called functionalized element-block materials[9] such as cross-linking, energetic, and Janus-type polymers in polymer chemistry,[10,11] chemical probes, and pharmaceuticals in chemical biology and life sciences.[12,13] However, although global azide-click conjugation of the same components has been well-documented, site-specific conjugation remains limited in multicomponent integration.[14,15] In particular, similar reactivities among alkyl azides lead to difficulty in site-specificity.

For discrimination of each azido position in multi-azides, suitable molecular structures have been studied (Fig. 2). Along with the different characters between alkyl and aryl (alkenyl) azides,[14,16] steric influence,[17,18] metal coordination,[19,20] and electron-poor aryl groups[21] are often utilized along with a

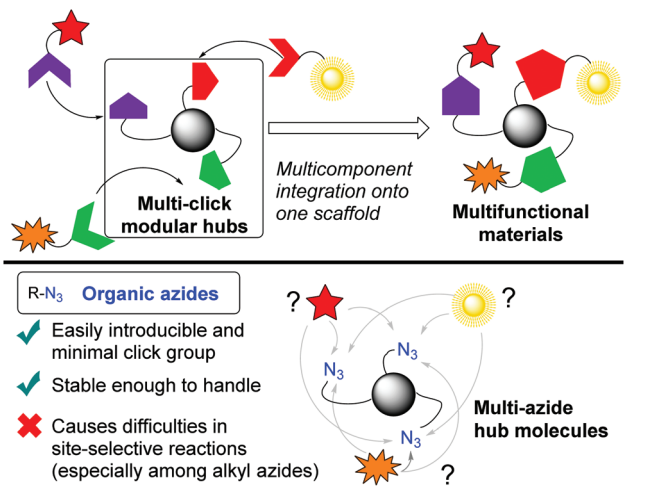

Fig. 1 The multi-click modular hub strategy toward multifunctional materials, and issues of multi-azides as modular hubs.

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†Electronic supplementary information (ESI) available: Experimental procedures, analytical data (^{1}H, ^{31}P, and ^{13}C NMR, IR, and mass spectroscopy, melting points, optical rotation, and R_f values), and computational results of the compounds. See DOI: 10.1039/d1qo01088c

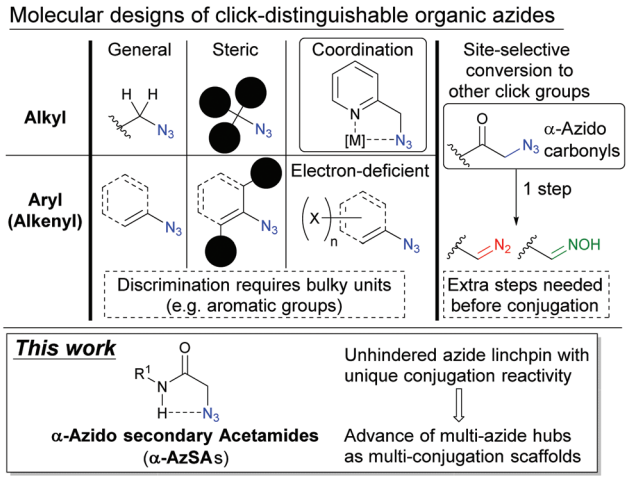


Fig. 2 Molecular designs of distinguishable organic azides toward multicomponent integration.

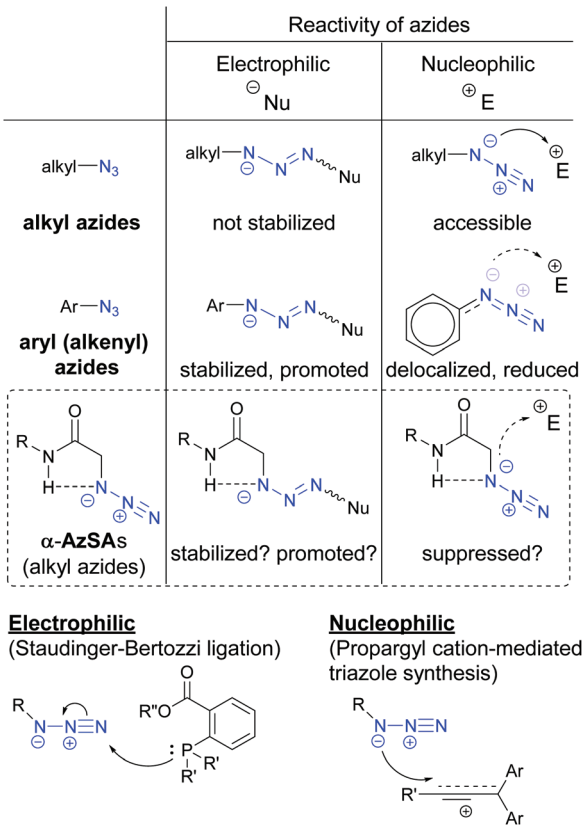


Fig. 3 General reactivity of organic azides and working hypothesis on α-AzSAs.

recently developed azide-protecting strategy.[22] However, discrimination of the azides mostly relies on the bulky substituents such as aromatic rings and *tert*-alkyl groups, and these could negatively impact the physiochemical properties and dynamics of the materials.[23,24] Thus, a new azide-discrimination strategy which does not require the help of bulky substituents should be investigated.

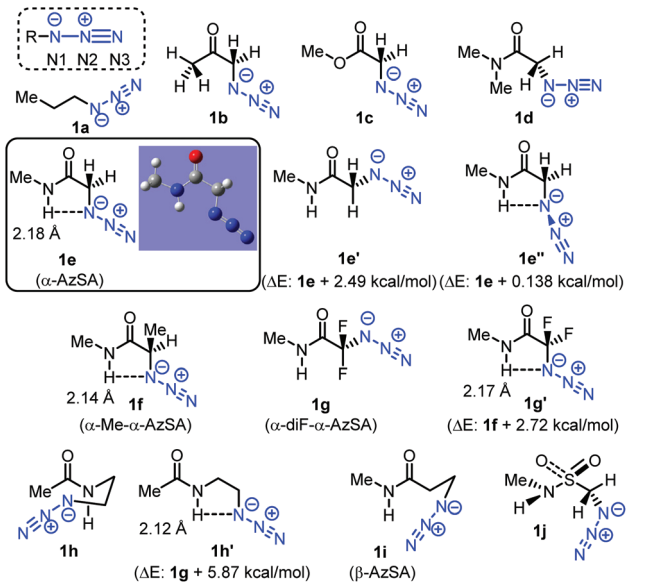
Focusing on multi-azide chemistry, we recently reported the site-selective conversion of azido groups at carbonyl α-positions to diazo or oxime click groups with the retention of other azide moieties and one-pot multi-component conjugation onto the triple-click scaffold converted from the tris (alkyl azide) compound.[15,25] Although our methods allow distinguishing multiple alkyl azido groups, the extra conversion step is undesired for conjugation. Inspired by metal-coordination[19] and the α-azido carbonyl strategy,[15] we envisioned that the intramolecular azide–NH interaction in α-azido secondary acetamides (henceforth simply "α-AzSAs")[26,27] could lead to unique reactivity without bulky substituents. Herein, we report α-AzSAs as minimal and unhindered azido units, which allow selective conjugation in the presence of other organic azides. We also showcase the site-selective integration of the functional components onto the diazide modular hubs.

Results and discussion

In general, unlike those of alkyl azides, electrophilic addition reactions of aryl (alkenyl) azides are favored because of the stabilized triazene intermediates (Fig. 3).[28] In contrast, nucleophilic reactions with aryl (alkenyl) azides are suppressed due to the low nucleophilicity caused by the delocalization. We hypothesized that intramolecular hydrogen bonding[29] in α-AzSAs could change the reactivity of alkyl azides. In other words, by the hydrogen interaction, α-AzSAs could be supposed to promote electrophilic reactions,[30,31] but suppress nucleophilic reactions. Although α-AzSAs, also described as secondary amides of azidoglycine, are general in click chemistry, their specificity has not been mentioned to the best of our knowledge. To evaluate the characteristics of α-AzSAs on the selective reaction in the presence of other alkyl azides, we chose the Staudinger–Bertozzi ligation reaction for the electrophilic reaction of azides.[32] For the nucleophilic reaction, we have developed propargyl cation-mediated rapid triazole synthesis through the nucleophilic addition of alkyl azides followed by cyclization.[33] Thus, we chose this method.

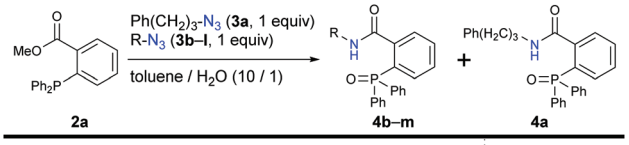
Prior to the synthesis, we began our study using DFT calculations to prove our hypothesis shown in Fig. 3 (Table 1, see also the ESI†).[34,35] From the obtained stable conformations, the direction of the C–N3 bonds of the ketone, ester, and secondary amide of α-azido carbonyl compounds **1b–d** is in the s-*trans* conformation. In contrast, tertiary amide **4** is an eclipsed conformation for its steric repulsion between azido and *N*-methyl groups. Alongside these s-*trans* conformations, we found that the charge density on the N1 atom of the azido group in α-AzSA **1e** increased compared to those of other compounds, especially among the amides. In the case of its conformers (**1e′** and **1e″**), the charge distribution value on the N1 atom of non-s-*trans* **1e′** is much decreased, whereas s-*trans* **1e″** retains a similar value. These suggest an interaction between the N1 atom in the azide group and the *N*-hydrogen atom in

Table 1 Calculated stable conformations of organic azides and charge distribution on their azido groups[a]



Entry	Compounds/ conformations	Mulliken charge distribution (a.u.) N1	N2	N3
1	**1a**	−0.284	+0.253	−0.167
2	**1b**	−0.310	+0.258	−0.151
3	**1c**	−0.268	+0.259	−0.154
4	**1d**	−0.295	+0.270	−0.140
5	**1e**	−0.333	+0.256	−0.145
6	**1e′**	−0.275	+0.260	−0.145
7	**1e″**	−0.312	+0.265	−0.144
8	**1f**	−0.329	+0.266	−0.147
9	**1g**	−0.292	+0.285	−0.093
10	**1g′**	−0.351	+0.274	−0.086
11	**1h**	−0.261	+0.255	−0.168
12	**1h′**	−0.319	+0.253	−0.148
13	**1i**	−0.272	+0.251	−0.184
14	**1j**	−0.261	+0.270	−0.129

[a] The DFT calculations performed with the Gaussian09 suite of programs using the dispersion-corrected B3LYP-D3 density functional with the 6-311G** basis set.

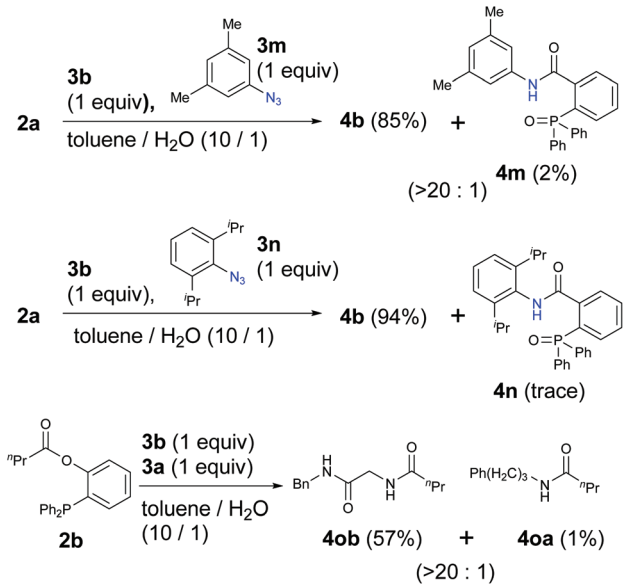


R-N_3	Yields[a] 4b–l (3b–l)	4a (3a)	Ratio (4b–l : 4a)
R' = Bn (**3b**)	93% (7%)	4% (69%)	>20 : 1
R' = Cy (**3c**)	88% (9%)	6% (70%)	15 : 1
R' = Ph_2CH (**3d**)	91% (7%)	3% (58%)	>20 : 1
R' = Ph (**3e**)	96% (3%)	3% (88%)	>20 : 1
3f	76% (17%)	14% (39%)	5.4 : 1
3g	60% (33%)	32% (50%)	1.9 : 1
3h	74% (21%)	27% (64%)	2.7 : 1
R' = NBn_2 (**3i**)	76% (14%)	16% (63%)	4.8 : 1
R' = OBn (**3j**)	54% (16%)	10% (62%)	5.4 : 1
R' = Ph (**3k**)	48% (38%)	11% (54%)	4.4 : 1
3l	61% (0%)[b]	35% (38%)	1.7 : 1

Scheme 1 Competitive Staudinger–Bertozzi ligations (0.1 mmol scale). [a] Yield determined by ^{1}H NMR. [b] Not observed due to the volatility.

the amide group.[26] Propanamide of α-AzSA **1f** shows a similar stable conformation with an increased value on N1. Because a positive interaction with the dipolar azido group is unlikely, the NH–N1 interaction would be observed by the dipolar repulsion-induced stable s-*trans* conformation of the α-AzSA structure. Indeed, α-difluoroazidoacetamide **1g**, which is known to be isolable,[36] is s-*trans* between carbonyl and fluoride groups. Neither **1h** with azidoalkyl side chains nor β-AzSA **1i** shows any NH–N1 interaction. Unlike amides, sulfonamide **1j** does not show specific interactions due to the loss of planarity.[37] These results suggest the interaction between NH and the azide group, which influences the electronic situation of the azido group, and prompted us to use α-AzSAs as uniquely clickable azides.

We turned to a feasibility study by performing both electrophilic and nucleophilic reactions of various azides under competition with a general alkyl azide. First, we examined the Staudinger–Bertozzi ligation reaction with **2a** as an electrophilic reaction (Scheme 1).[32] Because the addition of phosphines to the organic azides is a reversible step, stabilization of phosphazide intermediates can improve the reaction progress. In the case of aryl azides of this reaction, stabilization of phosphazide from the aryl azides by hydrogen bonding with NH of the amide has been demonstrated.[38] With α-AzSAs of alkyl azides, as expected, ligation products **4b–e** from α-AzSAs **3b–e** were obtained almost predominantly (nearly >20 : 1 ratio) in excellent yields, even under competition with 3-phenylpropyl azide **3a**. α-AzSA **3f** of the secondary alkyl azide only showed moderate selectivity due to the steric influence at the stage of aza-ylide formation in the Staudinger reaction.[30,31] The low selectivity of **3g** with a β-azido group and **3h** with an azidoalkyl side chain[39] revealed the importance of azide positioning. Although the values are variable, the downfield chemical shifts of the N–H in ^{1}H NMR[26e,34,35,40] compared to those without the azido group would also suggest the hydrogen bonding of α-AzSAs. Despite the same α-azidocarbonyl structures, the ter-

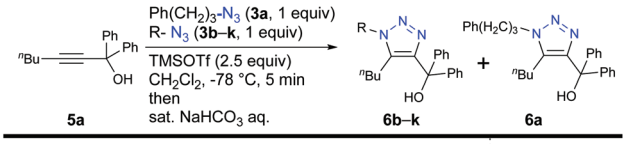


Scheme 2 Competitive Staudinger–Bertozzi ligation with aryl azides and application to the traceless reaction (0.1 mmol scale; yield determined by ^{1}H NMR).

tiary amide, ester, and ketone **3i–k** gave **4i–k** with only moderate selectivity. Benzyl azide **3l** did not show specific selectivity.

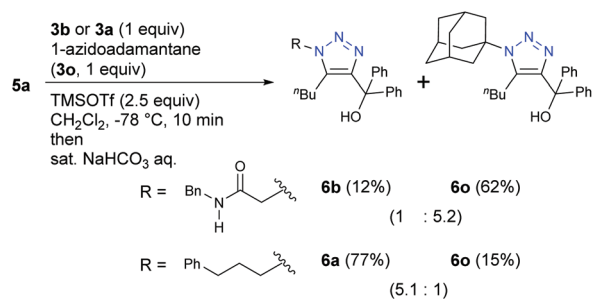
Because aryl azides have been known to exhibit strong reactivity in the Staudinger reaction or ligation, we also examined the competitive reactions with α-AzSA **3b** and aryl azides **3m** and **3n** (Scheme 2). Interestingly, α-AzSA **3b** also produced the corresponding compounds with excellent selectivity rather than aryl azide **3m**. α-AzSA **3b** also underwent the Staudinger ligation prior to the sterically hindered but uniquely reactive aryl azide **3n**.[18] In addition, this selectivity was also observed in traceless Staudinger ligation.[41]

Encouraged by the positive reactivity of the electrophilic behaviors, we moved to evaluate the nucleophilic characteristics of α-AzSAs by our developed propargyl cation-mediated triazole synthesis shown in Fig. 3 (Scheme 3).[33] With propargyl alcohol **5** and alkyl azide **3a**, we examined the competitive reaction followed by aqueous quenching for the introduction of the hydroxy group. As expected, the reactivities of *N*-benzyl and *N*-cyclohexyl α-AzSAs **3b** and **3c** were very low compared to that of **3a**, and most of the starting α-AzSAs were recovered. On the other hand, **3a** was converted to triazole **6a** in excellent yields. The observed excellent selectivity (1 : >20 ratio) was inverse to that of Staudinger–Bertozzi ligation (Schemes 1 and 2). **3d** with a bulky side chain showed moderate selectivity, but the selectivity was improved in toluene. Unexpectedly, *N*-phenyl α-AzSA **3e** did not show selectivity in dichloromethane, and the reaction suppression by toluene solvent was not satisfactory. Secondary alkyl α-AzSA **3f** also exhibited good selectivity (1 : 17), whereas β-AzSA **3g** or *N*-azidoalkyl amide **3h** did not. The selectivities of the tertiary amide, ester, ketone, and benzyl azides **3i–l** were moderate or not observed. This reaction strongly depends on the nucleophilicity of azido groups. Thus, general aryl azides did not afford the products because

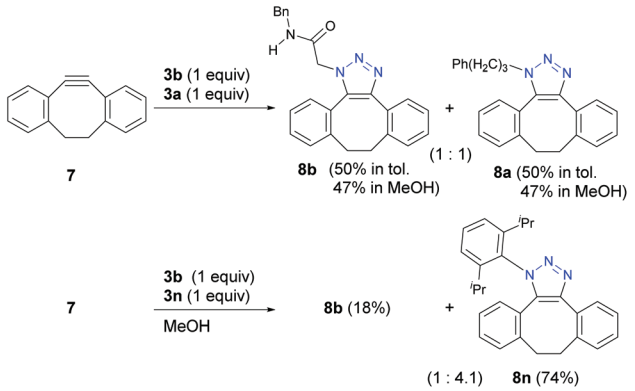


R-N_3	Yields (%)[a] 6b–l (3b–l)	6a (3a)	Ratio (6b–l : 6a)
R' = Bn (**3b**)	3% (93%)	86% (8%)	1 : >20
R' = Cy (**3c**)	1% (98%)	89% (11%)	1 : >20
R' = Ph_2CH (**3d**)	10% (70%)	83% (16%)	1 : 8.3
	[2% (92%)	61% (20%)	1 : >20]^b
R' = Ph (**3e**)	31% (67%)	46% (48%)	1 : 1.5
	[8% (92%)	63% (32%)	1 : 7.9]^b
3f	5% (93%)	86% (5%)	1 : 17
3g	12% (84%)	84% (14%)	1 : 7.0
	[33% (64%)	50% (47%)	1 : 1.5]^b
3h	9% (80%)	72% (7%)	1 : 8.0
	[20% (53%)	35% (33%)	1 : 1.8]^b
R' = NBn_2 (**3i**)	15% (85%)	80% (13%)	1 : 5.3
	[11% (69%)	58% (28%)	1 : 5.3]^b
R' = OBn (**3j**)	16% (74%)	61% (20%)	1 : 3.8
R' = Ph (**3k**)	42% (58%)	51% (49%)	1 : 1.2
	[40% (35%)	30% (59%)	1 : 0.8]^b
3l	52% (—)[c]	41% (53%)	1 : 0.8

Scheme 3 Competitive propargyl cation-mediated triazole formation reactions with propargyl alcohol **5a** (0.1 mmol scale). [a] Yield determined by ^{1}H NMR. [b] Reaction in toluene. [c] Not determined due to the volatility.



Scheme 4 Competitive propargyl cation-mediated triazole formation reactions with azidoadamantane of bulky *tert*-alkyl azide (0.1 mmol scale; isolated yields).

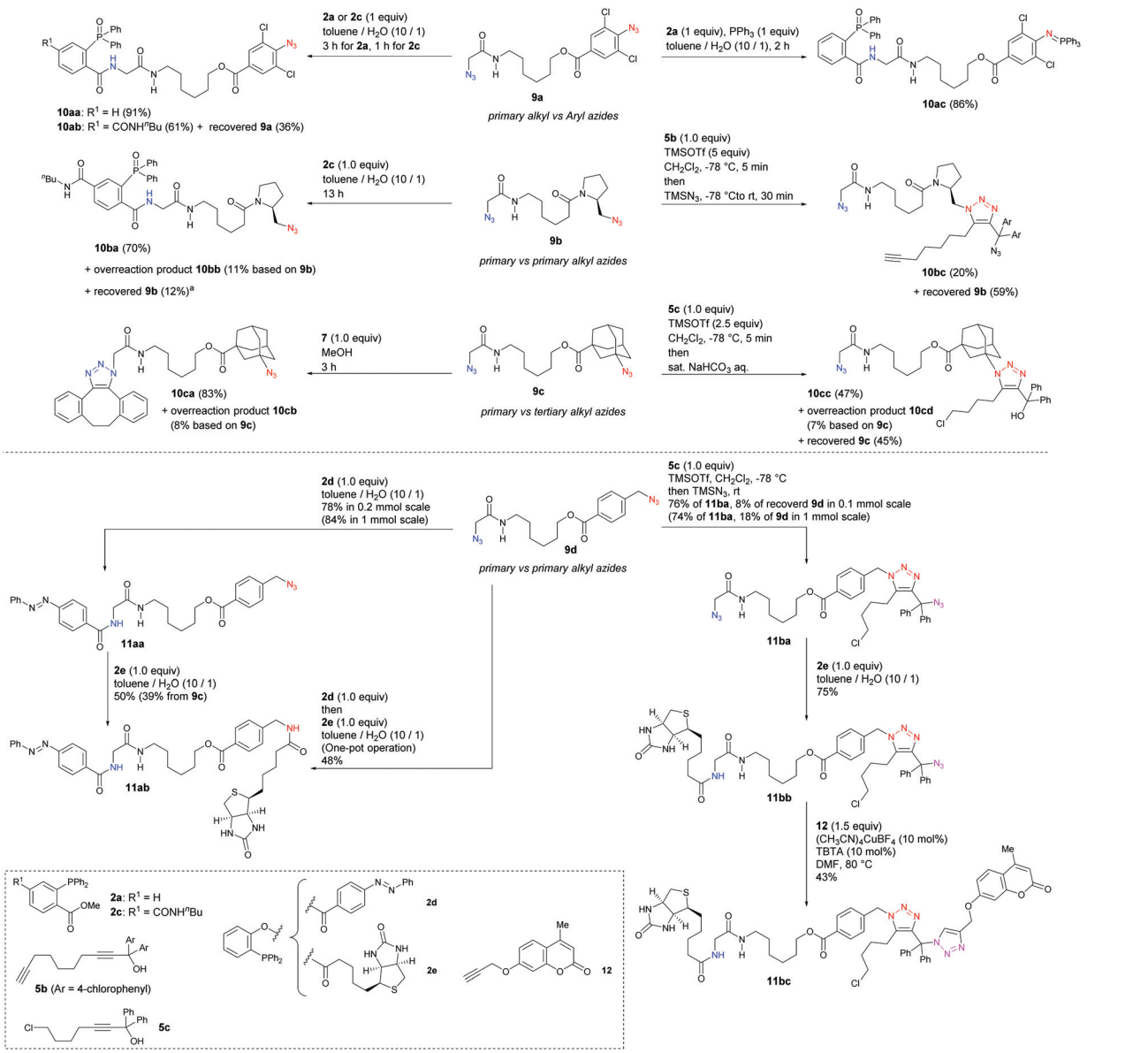


Scheme 5 Strain-promoted azide-alkyne cycloaddition (SPAAC) reactions (0.1 mmol scale; yield determined by ^{1}H NMR except for **8n** (isolated yield)).

of the lack of nucleophilicity by the delocalization (Fig. 3).[33a] For this reason, we did not test aryl azides in this reaction.

The specificity of α-AzSAs was also demonstrated with bulky tertiary alkyl azide **3o** (Scheme 4). While the reaction with **3a** and **3o** gave less-hindered **6a** from **3a** as a major product, bulky **6o** from **3o** was obtained as a major product under competition with primary alkyl α-AzSA **3b**. These results indicate that the α-AzSA skeleton is a primary alkyl azide that can exhibit high selectivity by both promoting electrophilic reactions and inhibiting nucleophilic reactions.

However, unlike the tested stepwise reactions, strain-promoted azide–alkyne cyclization (SPAAC) of pericyclic reaction[42] with **7** showed no selectivity (Scheme 5). This result indicates that the azido groups in α-AzSAs retain the same 1,3-dipolar reactivity as general alkyl azides. Indeed, the reaction with **3a**



Scheme 6 Site-selective use of azido groups in α-AzSA-containing diazides. Isolated yield except for recovered **9b** (^{1}H NMR yield) in the reaction from **9b** to **10ba** due to the difficulty of purification. TBTA: tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine.

and a bulky **3n** gave **8n** in a similar ratio to the reported values.[18a,b] On the other hand, very recently, Raines and co-workers reported the SPAAC with the novel aza-dibenzocyclooctyne.[26e] Although competitive reactions were not examined, the reaction rate constants showed the fast SPAAC reaction of α-AzSA **3b** compared to other alkyl azides. The inter- and intramolecular hydrogen bonding of **3b** with the alkyne are also suggested in the transition state. Thus, the azide-hydrogen-bonding-assisted selective conjugation approach should also work in the pericyclic reaction by developing the molecular design of azidophiles.

Having identified the unique reactivities of α-AzSAs, we examined the site-selective conjugation of diazides containing an α-AzSA structure (Scheme 6). For a diazide of aryl and α-AzSA **9a**, Staudinger–Bertozzi ligation occurred at the α-AzSA moiety selectively. With a 2,6-dichloro azido benzene unit forming stable aza-ylides,[21e] the one-pot double Staudinger reaction also successfully gave **10ac**. Next, bis(alkylazido) compounds, which face difficulty in undergoing site-selective conjugation, were investigated. α-AzSA-selective ligation of **9b** was accomplished in 70% yield with 11% of overreacted **10bb**. On the other hand, alkyl azide-selective triazole synthesis was achieved to give **10bc** without the overreaction byproduct, although the azide close to *tert*-amide was also unreactive. With **9c** consisting of primary and tertiary alkyl azides, SPAAC[42] occurred only at the α-AzSA moiety owing to the steric hindrance. Nevertheless, by our method,[33] we could reverse this selectivity to obtain **10cb** of the bulky azide-reacted triazole in 43% yield with the recovered **9c** in 47% yield. Longer reaction time led to decomposition of **9c** and **10cc** by the generation of the tertiary carbocation. Although not perfect, we demonstrated a way to the prior use of the sterically hindered azide even in the presence of unmasked and unhindered azides. In all cases, one-on-one adducts at the opposite azide positions were not observed.

Finally, we sought to showcase the site-selective conjugation of functional groups onto the bis(primary alkyl azide) compound **9d** (Scheme 6). The traceless Staudinger ligation[41] achieved the prior use of the α-AzSA moiety to attach the fluorescent azobenzene moiety to give **11aa** followed by the conjugation at the benzylic position with biotin **2e**. The conjugation from **9d** to **11ab** was also successful in one pot. In contrast, selective conjugation at the benzylic azide was demonstrated by three-component coupling with chloroalkyl propargyl alcohol **5c** followed by azidation[33a,b] to give diazide **11ba**. The first steps of each selective conjugation reaction were also successful on large scale (1 mmol). To the less-hindered α-AzSA moiety in **11ba**, **2e** was attached selectively. Lastly, CuAAC of the highly hindered triarylmethyl azide[16b,43,44] in **11bb** with the propargyl ether of the fluorescent unit **12** was accomplished to afford **11bc**.

Conclusions

In summary, we reported the unique reactivities of the α-AzSA structure as a minimal and unhindered azido unit. The amide–NH–azide interaction in the α-AzSA, supposed by DFT calculations, allowed selective conjugation in the presence of other organic azides. With Staudinger–Bertozzi ligation, α-AzSAs could conjugate prior to the other primary alkyl azides. On the other hand, in the case of propargyl cation-mediated triazole synthesis we have developed, α-AzSAs remained inert, and other alkyl azides, including even tertiary alkyl azides, underwent the conjugation. We also demonstrated site-selective integration of the functional components onto the diazide modular hubs. The unique characteristics of α-AzSAs[44] would open a new methodology of discriminative azide click reaction free from bulky substituents. We also believe that this work could help develop multifunctional chemical probes and polymer materials. Further research based on this strategy is currently underway in our group.

Author contributions

KM and SO performed the synthetic experiments and collected the analytical data. HT conceptualized this project, performed the computational study, checked the collected analytical data and performed supervision. TT (molecular design for chemical biology), TM (synthesis), and KK (photochemical analysis) contributed to the discussion on this project, especially from the viewpoint of each research area. The first draft was written by HT, KM, and SO, and all authors contributed to the review.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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