Taming Unhindered Alkyl Azides by Intramolecular Hydrogen-Azide Interaction for Discriminative Conjugation onto Alkyl Diazides.

Koshiro Maegawa,[a] Hiroki Tanimoto,[a,b]* Seiji Onishi,[a] Takenori Tomohiro,[b] Tsumoru Morimoto,[a] and Kiyomi Kakiuchi[a]

[a]Division of Materials Science, Nara Institute of Science and Technology (NAIST), 8916-5 Takayamacho, Ikoma, Nara 630-0192, Japan.

[b]Faculty of Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan

ABSTRACT: 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 the 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 calculation, allowed selective conjugation in the presence of other azido moieties. With Staudinger-Bertozzi ligation, α-AzSAs proceeded the 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 discriminative integration of the functional components onto the diazide modular hubs.

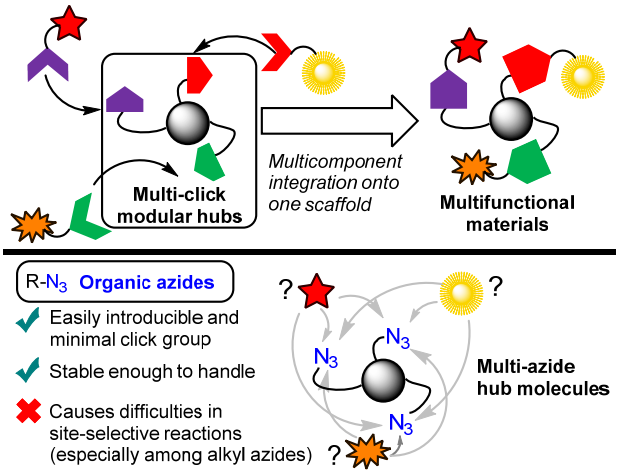


Figure 1. Multi-click Modular Hub Strategy Toward Multifunctional Materials, and Issues of Multi-Azides as Modular Hubs.

In a broad range of scientific areas, including chemical biology and polymer synthesis,[1,2] click chemistry[3] represented by organic azides[4] received much attention, which conjugates 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 (Figure 1). 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.[6,7] For these reasons, multi-azides could serve so-called functionalized element-block materials[8] such as cross-linking, energetic, Janus-type polymers in polymer chemistry,[9,10] chemical probes, and pharmaceuticals in chemical biology and life sciences.[11,12] However, although global azide-click conjugation of the same components has been well-documented, site-specific conjugation remains limited in multicomponent integration.[13,14] Especially, the similar reactivities among alkyl azides give difficulty on site-specificity.

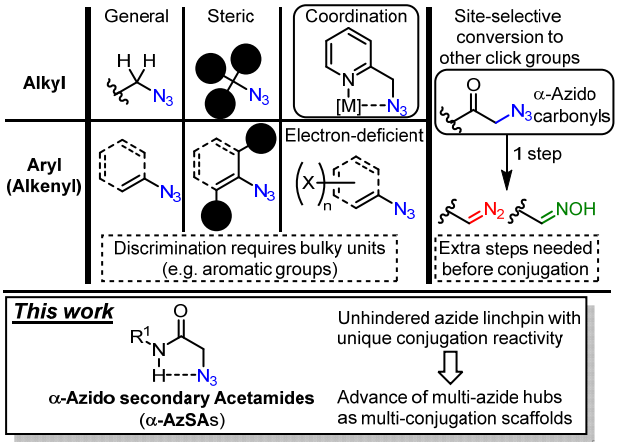


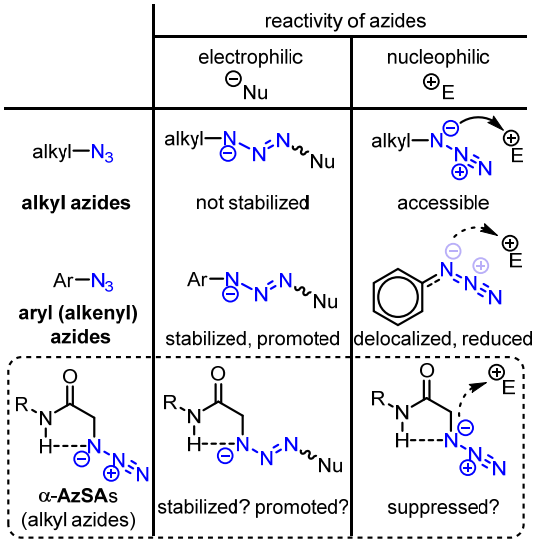
Figure 2. Molecular Designs of Distinguishable Organic Azides Toward Multicomponent Integration.

For discrimination of each azido position in multi-azides, suitable molecular structures have been studied (Figure 2). Along with the different nature between alkyl and aryl (alkenyl) azides,[13,15] steric influence,[16,17] metal coordination,[18,19] and electron-poor aryl groups[20] are often utilized

along with recently developed azide-protecting strategy.[21] 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.[22,23] Thus, a new azide-discrimination strategy free from the help of the bulky substituents should be investigated.

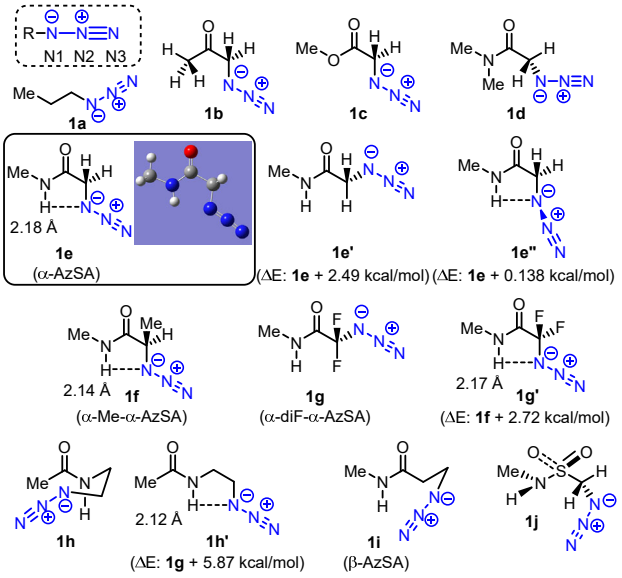
Focusing on multi-azide chemistry, we recently reported the site-selective conversion of azido groups at carbonyl α-positions to diazo or oxime click groups with retention of another azide moieties and the one-pot multi-component conjugation onto the triple-click scaffold converted from the tris(alkyl azide) compound.[14,24] Although our methods allow multiple alkyl azido groups distinguishable, extra conversion step is undesired for conjugation. Inspired by metal-coordination[18] and α-azido carbonyl strategy,[14] we envisioned that the intramolecular azide-NH interaction in α-azido secondary acetamides (α-AzSAs)[25,26] could serve 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 discriminative integration of the functional components onto the diazide modular hubs.

Chart 1. General Reactivity of Organic Azides and Working Hypothesis on α-AzSAs.



In general, unlike alkyl azides, electrophilic addition reactions of aryl (alkenyl) azides are favored because of the stabilized triazene intermediates (Chart 1).[27] In contrast, nucleophilic reactions with aryl (alkenyl) azides are suppressed due to the low nucleophilicity by the delocalization. We hypothesized that intramolecular hydrogen bonding[28] 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,[29,30] but to 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.

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

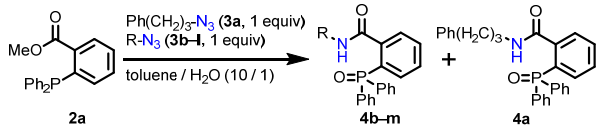
[a]The DFT calculations performed with the Gaussian09 suite of programs using the dispersion-corrected B3LYP-D3 density functional with the 6-311G** basis set.

To prove our hypothesis, we began our study from DFT calculation (Table 1, see also Supporting Information).[31,32] From the obtained stable conformations, the direction of C-N3 bonds of ketone, ester, and secondary amide of α-azido carbonyl compounds **1b–d** are in s-*trans*. In contrast, tertiary amide **4** is eclipsed conformation for its steric repulsion between azido and *N*-methyl groups. Alongside these s-*trans* conformations, we found that charge density on N1 atom of azido group in α-AzSA **1e** gained compared to other compounds, especially among the amides. In the case of its conformers (**1e'** and **1e"**), the charge distribution value on N1 atom of non-s-*trans* **1e'** is much decreased, whereas s-*trans* **1e"** keeps similar. These should suggest an interaction between the N1 atom in the azide group and the *N*-hydrogen atom in the amide group.[25] Propanamide of α-AzSA **1f** shows similar stable conformation with increased value on

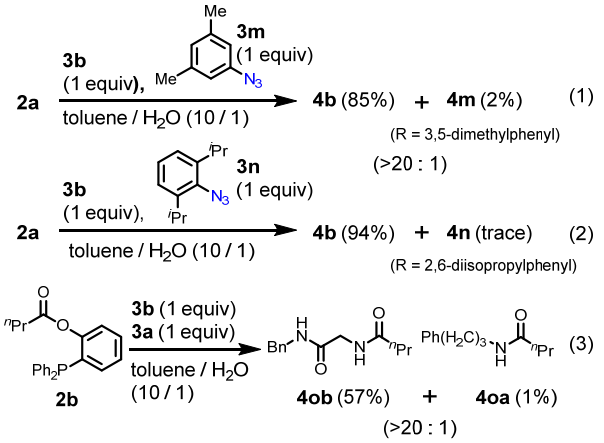
N1. Because a positive interaction with the dipolar azido group is unlikely, the NH-N1 interaction would be observed by the dipolar repulsion-induced stable s-*trans* conformation of the α-AzSA structure. Indeed, α-difluoroazidoacetamide **1g**, which is known to be isolable,[33] is s-*trans* between carbonyl and fluoride groups. Neither **1h** with azidoalkyl side chains nor β-AzSA **1i** show any NH-N1 interaction. Unlike amides, sulfonamide **1j** does not show specific interactions due to the loss of planarity.[34] These results suggest the interaction between NH and 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 both electrophilic and nucleophilic reactions of various azides under competition with a general alkyl azide. First, we examined Staudinger-Bertozzi ligation reaction with **2a** as an electrophilic reaction (Scheme 1).[35] 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 phoshazide from aryl azide by hydrogen bonding with NH of amide has been demonstrated.[36] 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 Staudinger reaction.[29,30] The low selectivity of **3g** with β-azido group and **3h** with azidoalkyl side chain[37] revealed the importance of azide positioning. Although the values are variable, the downfield chemical shifts of the N-H in ^{1}H NMR[25e,38] compared to those without the azido group would also suggest the hydrogen bonding of α-AzSAs. Despite the same α-azidocarbonyl structures, tertiary amide, ester, and ketone **3i–k** gave **4i–k** in only moderate selectivity. Benzyl azide **3l** did not show specific selectivity. In the competitive reactions with aryl azides **3m,n**, α-AzSA **3b** produced the corresponding compounds in excellent selectivity (eqs 1, 2). This selectivity was also observed in traceless Staudinger ligation (eq 3).[39]

Scheme 1. Competitive Staudinger-Bertozzi Ligations[a]



R-N_3	Yields[a] 4b–l (3b–l)	Yields[a] 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
Bn, N, H, Me **3f**	76% (17%)	14% (39%)	5.4 : 1
Bn, N, H **3g**	60% (33%)	32% (50%)	1.9 : 1
Ph, N, H **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
Ph **3l**	61% (0%)[b]	35% (38%)	1.7 : 1

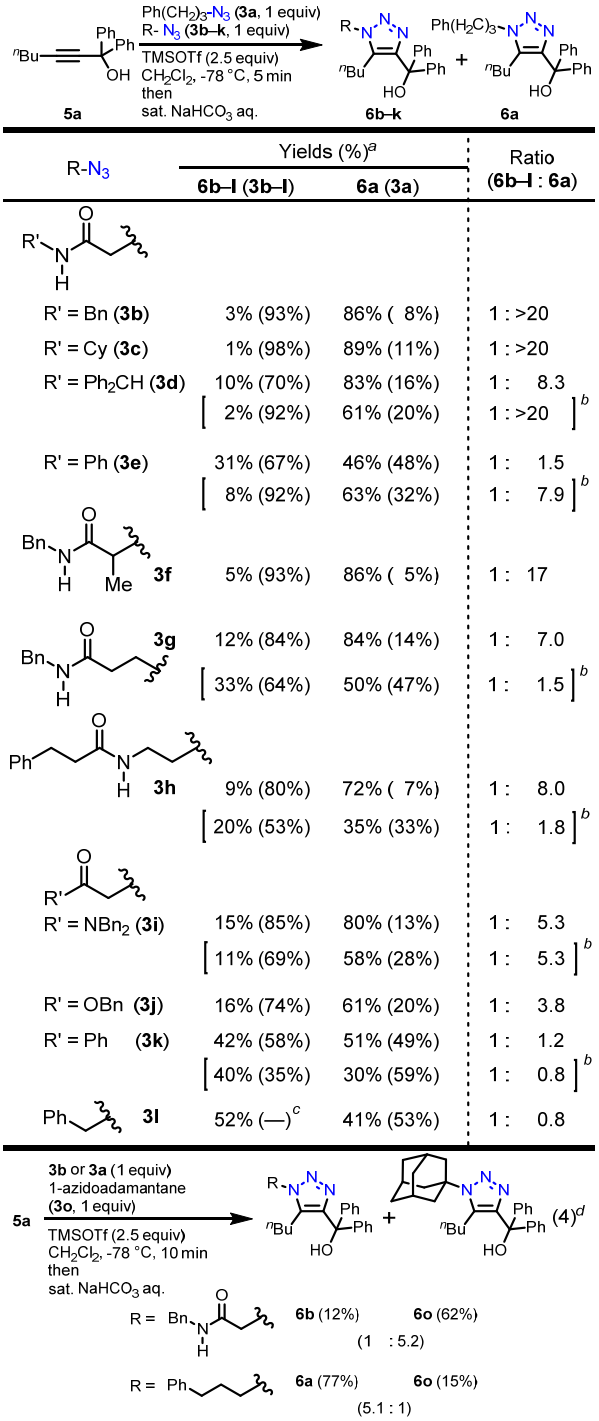


[a]0.1 mmol scale. Yield determined by ^{1}H NMR. [b]Not observed due to the volatility.

Encouraged by the positive reactivity of the electrophilic behaviors, we moved to evaluate the nucleophilic characteristics of α-AzSAs (Scheme 2). Previously, we developed propargyl cation-mediated triazole synthesis with organic azides by way of the nucleophilic addition to the propargyl cation followed by cyclization.[40,41] With propargyl alcohol **5** and α-AzSA **3a**, we examined competitive reaction followed by aqueous quench for introduction of the hydroxy group. As expected, the reactivities of *N*-benzyl and *N*-cyclohexyl

α-AzSAs **3b,c** 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 inversed to that of Staudinger-Bertozzi ligation (Scheme 1). **3d** with 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 tertiary amide, ester, ketone, and benzyl azides **3i–l** were moderate or not observed. The specificity of α-AzSAs was also demonstrated with bulky tertiary alkyl azide **3o** (Eq 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.

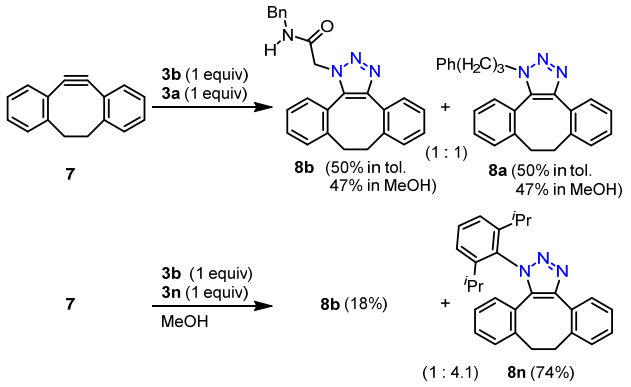
Scheme 2. Competitive Carbocation-Mediated Triazole Formation Reactions with Propargyl Alcohols[a]



[a]0.1 mmol scale. Yield determined by ^{1}H NMR. [b]Reaction in toluene. [c]Not determined due to the volatility. [d]Isolated yield.

On the other hand, unlike the tested stepwise reactions, strain-promoted azide-alkyne cyclization (SPAAC) of pericyclic reaction[42] with **7** showed no selectivity (Scheme 3).[25e] This result indicates that the azido groups in α-AzSAs retain the same 1,3-dipolar reactivity to general alkyl azides. Indeed, the reaction with **3a** and a bulky **3n** gave **8n** in a similar ratio to the reported values.[17a,b]

Scheme 3. SPAAC Reactions[a]

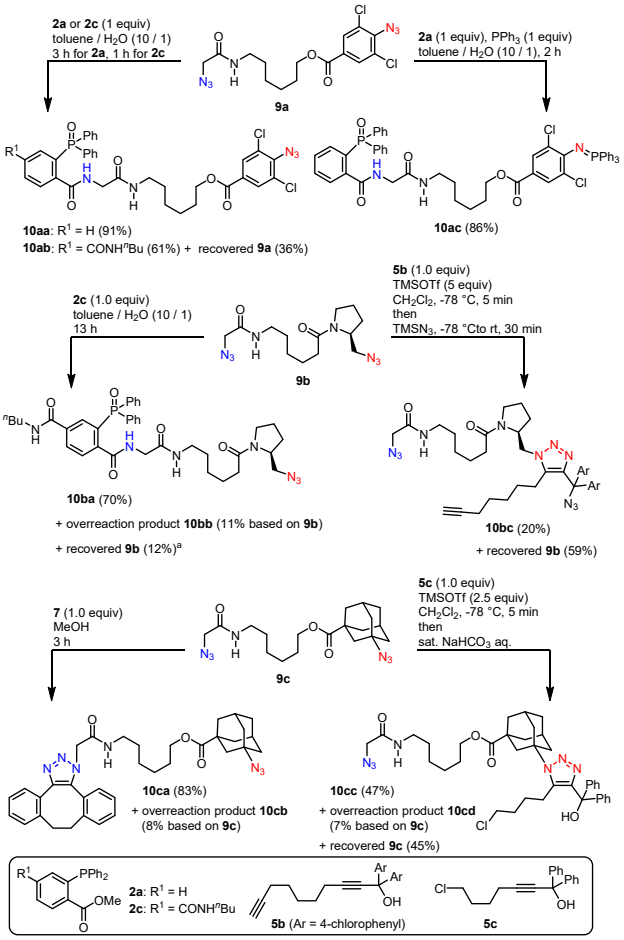


[a]0.1 mmol scale. Yield determined by ^{1}H NMR except for **8n** (isolated yield).

Having identified the unique reactivities of α-AzSAs, we examined the site-selective conjugation of diazides containing α-AzSA structure (Scheme 4). 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,[20e] one-pot double Staudinger reaction was also successful to give **10ac**. Next, bis(alkylazido) compounds were investigated, which have been difficult for discriminative conjugation. 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** consisted of primary and tertiary alkyl azides, SPAAC[42] occurred only at the α-AzSA moiety by following the steric hindrance (Scheme 3). Nevertheless, by our method,[40] we could reverse this selectivity to obtain **10cb** of the bulky azide-reacted triazole in 43% with the recovered **9c** in 47% yields. Longer reaction time decomposed **9c** and **10cc** by the generation of tertiary carbocation. Although not perfect, we demonstrated the way to the prior use of the sterically hindered azide even in the presence of unmasked and unhindered azide. In all cases, one-on-one adducts at the opposite azide positions were not observed.

Scheme 4. Site-Selective Use of Azido Groups in α-AzSA-containing diazides[a]

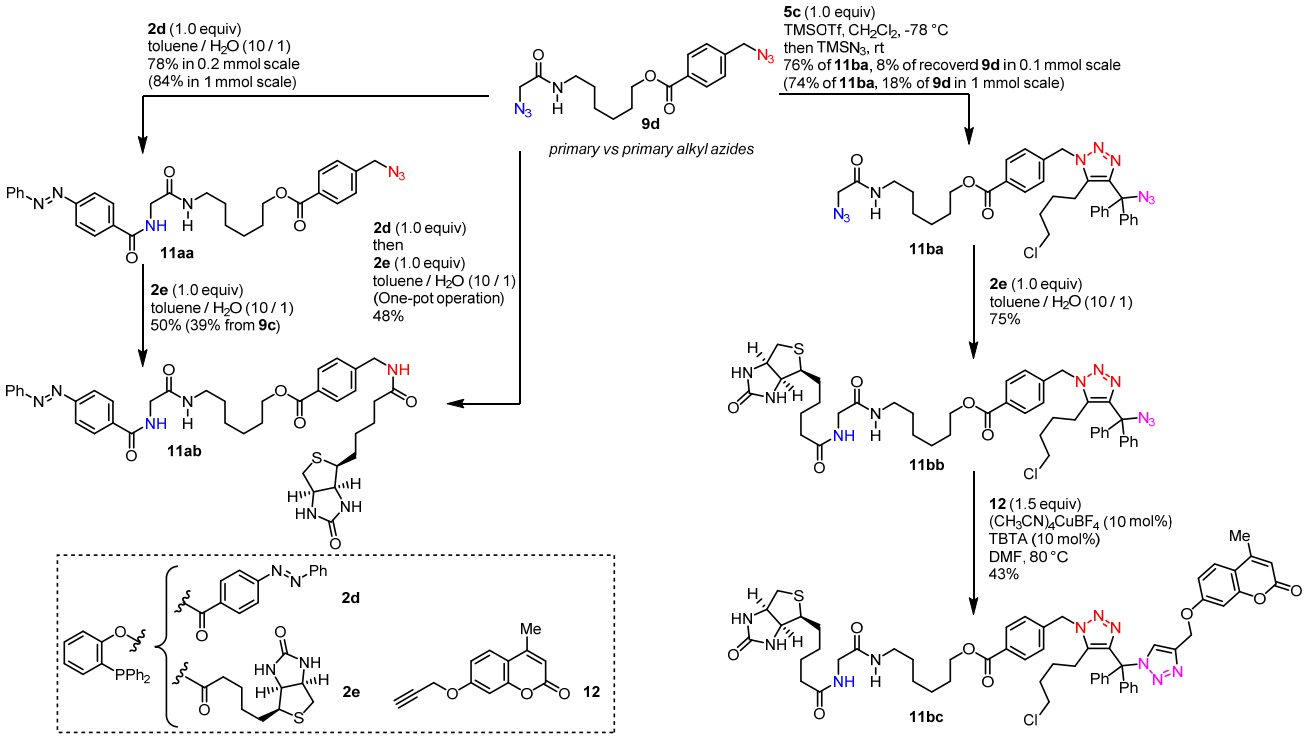


[a]Isolated yield except for recovered **9b** (^{1}H NMR Yield) in the reaction to **10ba** due to the difficulty of purification.

Finally, we sought to showcase the site-selective conjugation of functional groups onto the bis(primary alkyl azide) compound **9d** (Scheme 5). The traceless Staudinger ligation[39] achieved the prior use of 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. By contrast, selective conjugation at the benzylic azide was demonstrated by three-component coupling with chloroalkyl propargyl alcohol **5c** followed by azidation[40a,b] to give diazide **11ba**. To the less-hindered α-AzSA moiety in **11ba**, **2e** was attached selectively. Lastly, CuAAC of the highly hindered triarylmethyl azide[15b,43] in **11bb** with the propargyl ether of fluorescent unit **12** was accomplished to afford **11bc**.

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 calculation, 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 kept inert, and other alkyl azides, including even tertiary alkyl azides, underwent the conjugation. We also demonstrated discriminative integration of the functional

Scheme 5. Site-Selective Integration of Functional Compounds onto the Primary Alkyl Diazide[a]



[a]Isolated yield. TBTA: Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine.

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 develop multifunctional chemical probes and polymer materials. Further research based on this strategy is currently ongoing in our group.

ASSOCIATED CONTENT

The Supporting Information is available free of charge at http://pubs.acs.org.

Experimental procedures, analytical data (^{1}H, ^{31}P, ^{13}C NMR, IR, mass spectroscopy, melting point, optical rotation, and R_f value), and computational results of the compounds.

AUTHOR INFORMATION

Corresponding Author

*E-mail: tanimoto@pha.u-toyama.ac.jp

Notes

The authors declare no competing financial interest.

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