

RESEARCH ARTICLE

[View Article Online](#)
[View Journal](#) | [View Issue](#)



Cite this: *Org. Chem. Front.*, 2021, **8**, 5793

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

Koshiro Maegawa,^a Hiroki Tanimoto,^{ID *a,b} Seiji Onishi,^a Takenori Tomohiro,^{ID b} Tsumoru Morimoto^a and Kiyomi Kakiuchi^a

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.

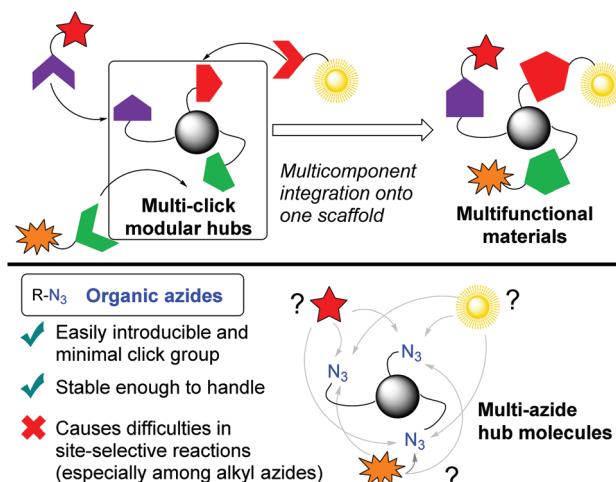
Received 25th July 2021,
Accepted 11th August 2021
DOI: 10.1039/d1qo01088c
rsc.li/frontiers-organic

Introduction

In a broad range of scientific areas, including chemical biology and polymer synthesis,^{1,2} click chemistry³ represented by organic azides⁴ 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 materials⁹ 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-selectivity.

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 groups²¹ are often utilized along with a



^aDivision of Materials Science, Nara Institute of Science and Technology (NAIST), 8916-5 Takayamacho, Ikoma, Nara 630-0192, Japan

^bFaculty of Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan. E-mail: tanimoto@pha.u-toyama.ac.jp

† Electronic supplementary information (ESI) available: Experimental procedures, analytical data (¹H, ³¹P, and ¹³C 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. 1 The multi-click modular hub strategy toward multifunctional materials, and issues of multi-azides as modular hubs.

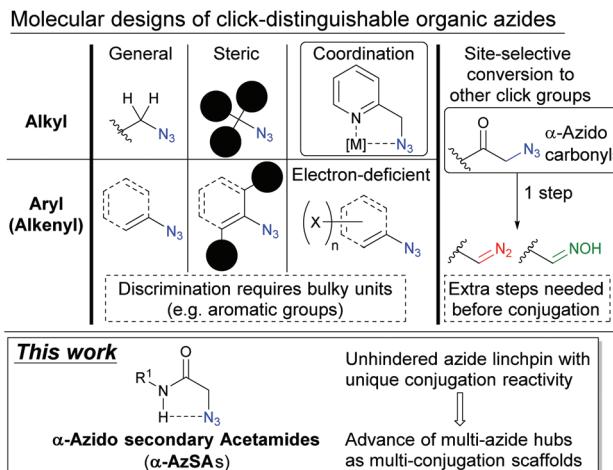


Fig. 2 Molecular designs of distinguishable organic azides toward multicomponent integration.

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-coordination¹⁹ 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 bonding²⁹ 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

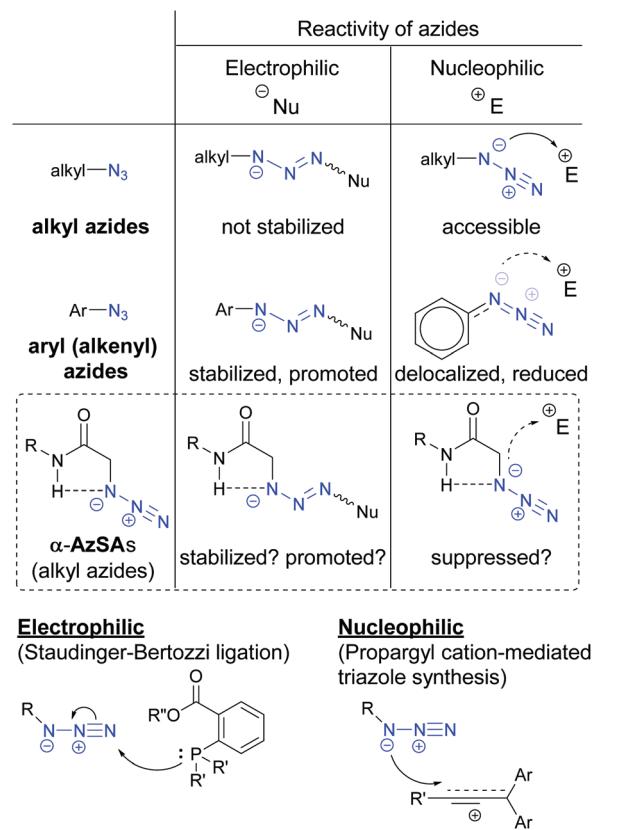


Fig. 3 General reactivity of organic azides and working hypothesis on α -AzSAs.

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 azido 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.

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 azido group, which influences the electronic situation of the azido group, and prompted us to use α -AzSAs as uniquely clickable azides.

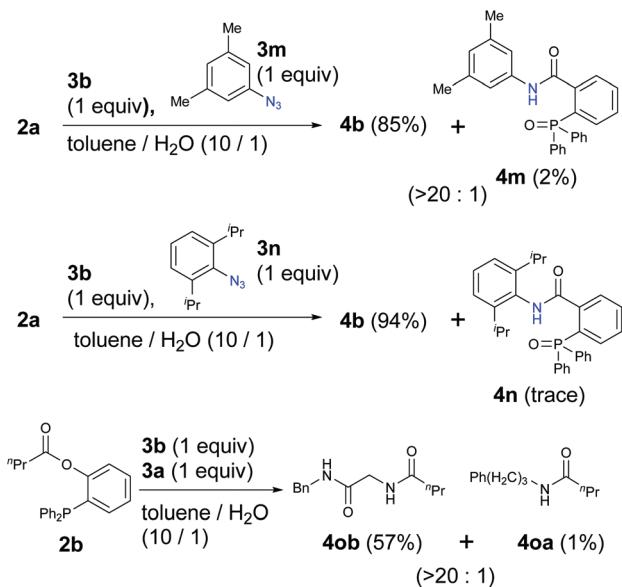
We turned to a feasibility study by performing both electrophilic and nucleophilic reactions of various azides under competition with a general alkyl azide. First, we examined the

2a	Ph(CH ₂) ₃ -N ₃ (3a, 1 equiv) R-N ₃ (3b–l, 1 equiv) toluene / H ₂ O (10 / 1)	Yields ^a		Ratio (4b–l : 4a)
		4b–l (3b–l)	4a (3a)	
	R' = Bn (3b)	93% (7%)	4% (69%)	>20 : 1
	R' = Cy (3c)	88% (9%)	6% (70%)	15 : 1
	R' = Ph ₂ CH (3d)	91% (7%)	3% (58%)	>20 : 1
	R' = Ph (3e)	96% (3%)	3% (88%)	>20 : 1
	Bn-NH-C(=O)-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NHC(=O)-Me 3f	76% (17%)	14% (39%)	5.4 : 1
	Bn-NH-C(=O)-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NHC(=O)-Ph 3g	60% (33%)	32% (50%)	1.9 : 1
	Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NHC(=O)-Ph 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-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NHC(=O)-Ph 3l	61% (0%) ^b	35% (38%)	1.7 : 1

Scheme 1 Competitive Staudinger–Bertozzi ligations (0.1 mmol scale).

^a Yield determined by ¹H NMR. ^b Not observed due to the volatility.

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 chain³⁹ revealed the importance of azide positioning. Although the values are variable, the downfield chemical shifts of the N–H in ¹H 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 ^1H NMR).

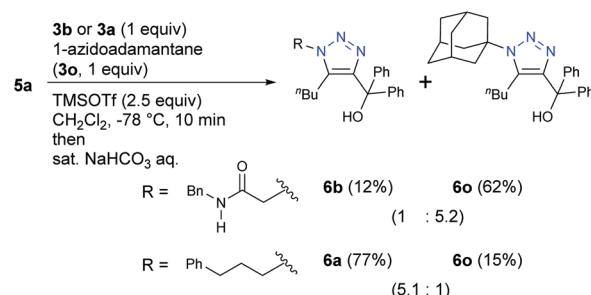
tertiary amide, ester, and ketone **3i–k** gave **4i–k** with only moderate selectivity. Benzyl azide **3l** did not show specific selectivity.

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

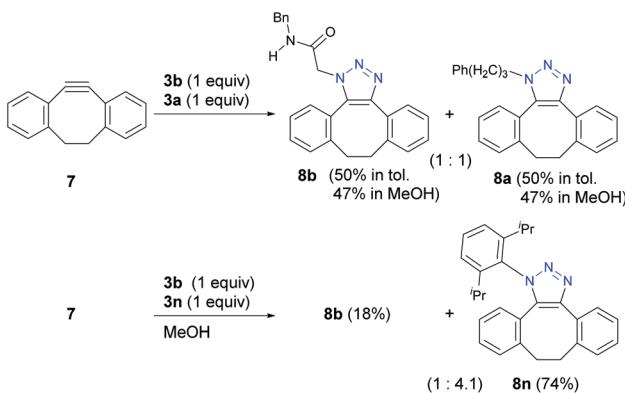
Encouraged by the positive reactivity of the electrophilic behaviors, we moved to evaluate the nucleophilic characteristics of α -AzSAs by our developed propargyl cation-mediated triazole synthesis shown in Fig. 3 (Scheme 3).³³ With propargyl alcohol **5a** and alkyl azide **3a**, we examined the competitive 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- <i>N</i> ₃	Yields (%) ^a		Ratio (6b–l : 6a)
	6b–l (3b–l)	6a (3a)	
<i>R'</i> = Bn (3b)	3% (93%)	86% (8%)	1 : >20
<i>R'</i> = Cy (3c)	1% (98%)	89% (11%)	1 : >20
<i>R'</i> = Ph ₂ CH (3d)	10% (70%)	83% (16%)	1 : 8.3
	2% (92%)	61% (20%)	1 : >20] ^b
<i>R'</i> = 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
3i	15% (85%)	80% (13%)	1 : 5.3
	11% (69%)	58% (28%)	1 : 5.3] ^b
3j	16% (74%)	61% (20%)	1 : 3.8
3k	42% (58%)	51% (49%)	1 : 1.2
	40% (35%)	30% (59%)	1 : 0.8] ^b
3l	52% (—) ^c	41% (53%)	1 : 0.8

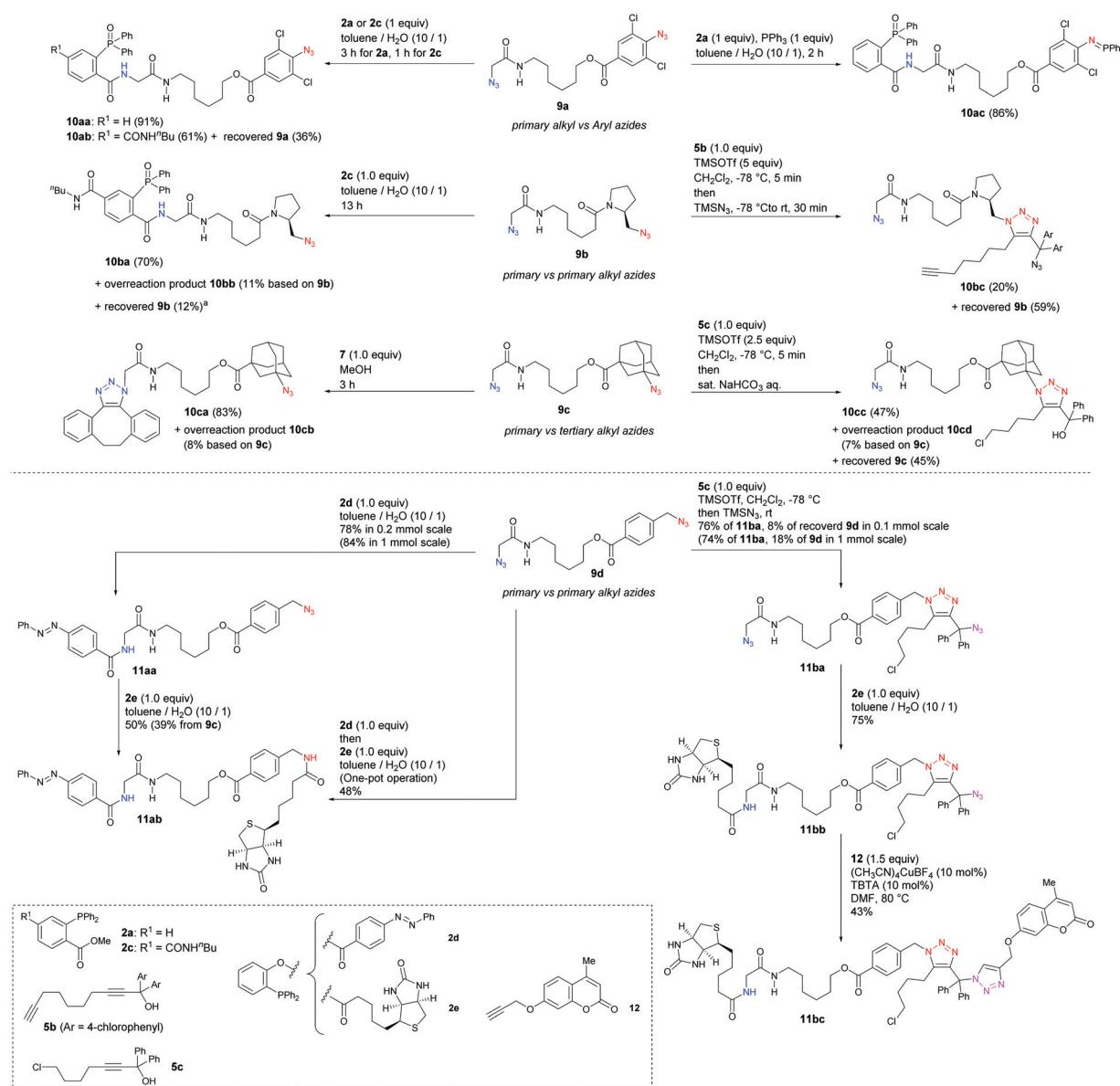
Scheme 3 Competitive propargyl cation-mediated triazole formation reactions with propargyl alcohol **5a** (0.1 mmol scale). ^a Yield determined by ^1H NMR. ^b Reaction in toluene. ^c Not determined due to the volatility.



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 ^1H NMR except for **8n** (isolated yield)).



Scheme 6 Site-selective use of azido groups in α -AzSA-containing diazides. Isolated yield except for recovered **9b** (^1H 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.

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 reaction⁴² 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**

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, SPAAC⁴² 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 ligation⁴¹ 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 triaryl methyl 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 -AzSAs⁴⁴ 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

This work was supported in part by Iketani Science and Technology Foundation (0321124-A), Firstbank of Toyama Scholarship Foundation Research Grant, and JSPS grant KAKENHI (C, JP18K05460). We acknowledge Assoc. Prof. Miho Hatanaka of Keio University for her helpful discussion on our DFT calculations and Assoc. Prof. Suguru Yoshida of Tokyo University of Science for his fruitful advice on click reactions. We also thank Ms Yoshiko Nishikawa and Ms Mieko Yamagaki (MS measurements) of NAIST.

Notes and references

- (a) N. J. Agard, J. M. Baskin, J. A. Prescher, A. Lo and C. R. Bertozzi, A Comparative Study of Bioorthogonal Reactions with Azides, *ACS Chem. Biol.*, 2006, **1**, 644–648; (b) E. Haldón, M. C. Nicasio and P. J. Pérez, Copper-catalysed Azide–alkyne Cycloadditions (CuAAC): An Update, *Org. Biomol. Chem.*, 2015, **13**, 9528–9550; (c) L. Zhu, C. J. Brassard, X. Zhang, P. M. Guha and R. J. Clark, On the Mechanism of Copper(I)-Catalyzed Azide–Alkyne

Cycloaddition, *Chem. Rec.*, 2016, **16**, 1501–1517; (d) E. Kim and H. Koo, Biomedical Applications of Copper-free Click Chemistry: in vitro, in vivo, and ex vivo, *Chem. Sci.*, 2019, **10**, 7835–7851.

2 (a) A. Qin, J. W. Y. Lamb and B. Z. Tang, Click Polymerization, *Chem. Soc. Rev.*, 2010, **39**, 2522–2544; (b) Y. Shi, X. Cao and H. Gao, The Use of Azide-alkyne Click Chemistry in Recent Syntheses and Applications of Polytriazole-based Nanostructured Polymers, *Nanoscale*, 2016, **8**, 4864–4881; (c) D. Huang, Y. Liu, A. Qin and B. Z. Tang, Recent Advances in Alkyne-based Click Polymerizations, *Polym. Chem.*, 2018, **9**, 2853–2867; (d) D. Huang, Y. Liu, A. Qin and B. Z. Tang, in *Click Polymerization*, ed. A. Qin, B. Z. Tang, The Royal Society of Chemistry, Croydon, 2018; (e) M. Schock and S. Bräse, Reactive & Efficient: Organic Azides as Cross-Linkers in Material Sciences, *Molecules*, 2020, **25**, 1009.

3 (a) *Click Chemistry for Biotechnology and Materials Science*, ed. J. Lahann, John Wiley & Sons, West Sussex, 2009; (b) H. C. Kolb, M. G. Finn and K. B. Sharpless, Click Chemistry: Diverse Chemical Function from a Few Good Reactions, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021; (c) C. W. Tornøe, C. Christensen and M. Meldal, Cu-Catalyzed Azide-Alkyne Cycloaddition, *Chem. Rev.*, 2008, **108**, 2952–3015; (d) M. F. Debets, C. W. J. van der Doelen, F. P. J. T. Rutjes and F. L. van Delft, Azide: A Unique Dipole for Metal-Free Bioorthogonal Ligations, *ChemBioChem*, 2010, **11**, 1168–1184; (e) E. M. Sletten and C. R. Bertozzi, From Mechanism to Mouse: A Tale of Two Bioorthogonal Reactions, *Acc. Chem. Res.*, 2011, **44**, 666–676; (f) D. M. Patterson, L. A. Nazarova and J. A. Prescher, Finding the Right (Bioorthogonal) Chemistry, *ACS Chem. Biol.*, 2014, **9**, 592–605; (g) A. Lossouarn, P.-Y. Renard and C. Sabot, Tailored Bioorthogonal and Bioconjugate Chemistry: A Source of Inspiration for Developing Kinetic Target-Guided Synthesis Strategies, *Bioconjugate Chem.*, 2021, **32**, 63–72.

4 (a) *Organic Azides: Synthesis and Applications*, ed. S. Bräse and K. Banert, John Wiley & Sons, West Sussex, 2010 For selected reviews published after this perspective book, see: (b) H. Tanimoto and K. Kakiuchi, Recent Applications and Developments of Organic Azides in Total Synthesis of Natural Products, *Nat. Prod. Commun.*, 2013, **8**, 1021–1034; (c) D. Intrieri, P. Zardi, A. Caselli and E. Gallo, Organic Azides: “Energetic Reagents” for the Intermolecular Amination of C–H Bonds, *Chem. Commun.*, 2014, **50**, 11440–11453; (d) X.-R. Song, Y.-F. Qiu, X.-Y. Liu and Y.-M. Liang, Recent Advances in the Tandem Reaction of Azides with Alkynes or Alkynols, *Org. Biomol. Chem.*, 2016, **14**, 11317–11331; (e) K. Wu, Y. Liang and N. Jiao, Azidation in the Difunctionalization of Olefins, *Molecules*, 2016, **21**, 352; (f) G. Huang and G. Yan, Recent Advances in Reactions of Azides, *Adv. Synth. Catal.*, 2017, **359**, 1600–1619; (g) R. Sala, C. Loro, F. Foschi and G. Broggini, Transition Metal Catalyzed Azidation Reactions, *Catalysts*, 2020, **10**, 1173.

5 (a) P. Lundberg, C. J. Hawker, A. Hult and M. Malkoch, Click Assisted One-Pot Multi-Step Reactions in Polymer Science: Accelerated Synthetic Protocols, *Macromol. Rapid Commun.*, 2008, **29**, 998–1015; (b) G. Viault, S. Dautrey, N. Maindron, J. Hardouin, P.-Y. Renard and A. Romieu, The First “Ready-to-use” Benzene-based Heterotrifunctional Cross-linker for Multiple Bioconjugation, *Org. Biomol. Chem.*, 2013, **11**, 2693–2705; (c) B. Thomas, M. Fiore, G. C. Daskhan, N. Spinellia and O. Renaudet, A Multi-ligation Strategy for the Synthesis of Heterofunctionalized Glycosylated Scaffolds, *Chem. Commun.*, 2015, **51**, 5436–5439; (d) G. C. Daskhan, C. Pifferi and O. Renaudet, Synthesis of a New Series of Sialylated Homo- and Heterovalent Glycoclusters by using Orthogonal Ligations, *ChemistryOpen*, 2016, **5**, 477–484; (e) A.-C. Knall, M. Hollauf, R. Saf and C. Slagovc, A trifunctional linker suitable for conducting three orthogonal click chemistries in one pot, *Org. Biomol. Chem.*, 2016, **14**, 10576–10580; (f) M.-L. Winz, E. C. Linder, J. Becker and A. Jäschke, Site-specific One-pot Triple Click Labeling for DNA and RNA, *Chem. Commun.*, 2018, **54**, 11781–11784; (g) Z. Li, S. Kosuri, H. Foster, J. Cohen, C. Jumeaux, M. M. Stevens, R. Chapman and A. J. Gormley, A Dual Wavelength Polymerization and Bioconjugation Strategy for High Throughput Synthesis of Multivalent Ligands, *J. Am. Chem. Soc.*, 2019, **141**, 19823–19830; (h) Y. Wang, J. Weng, J. Lin, D. Ye and Y. Zhang, NIR Scaffold Bearing Three Handles for Biocompatible Sequential Click Installation of Multiple Functional Arms, *J. Am. Chem. Soc.*, 2020, **142**, 2787–2794.

6 For recently published reviews on this strategy, see: (a) S. Yoshida, Sequential Conjugation Methods Based on Triazole Formations and Related Reactions Using Azides, *Org. Biomol. Chem.*, 2020, **18**, 1550–1562; (b) D. Sato, Z. Wu, H. Fujita, J. S. Lindsey, D. Sato, Z. Wu, H. Fujita and J. S. Lindsey, Design, Synthesis, and Utility of Defined Molecular Scaffolds, *Organics*, 2021, **2**, 161–273.

7 For recent review on preparation methods of aliphatic azides, see: P. Sivaguru, Y. Ning and X. Bi, New Strategies for the Synthesis of Aliphatic Azides, *Chem. Rev.*, 2021, **121**, 4253–4307.

8 (a) P. Biallas, J. Heider and S. F. Kirsch, Functional Polyamides with gem-Diazido Units: Synthesis and Diversification, *Polym. Chem.*, 2019, **10**, 60–64; (b) S. K. Boopathi, N. Hadjichristidis, Y. Gnanou and X. Feng, Direct Access to Poly(glycidyl Azide) and its Copolymers Through Anionic (Co-)polymerization of Glycidyl Azide, *Nat. Commun.*, 2019, **10**, 293. See also the references cited therein.

9 (a) Y. Chujo and K. Tanaka, New Polymeric Materials Based on Element-Blocks, *Bull. Chem. Soc. Jpn.*, 2015, **88**, 633–643; (b) M. Gon, K. Tanaka and Y. Chujo, Recent progress in the development of advanced element-block materials, *Polym. J.*, 2018, **50**, 109–126; (c) *New Polymeric Materials Based on Element-Blocks*, ed. Y. Chujo, Springer, Singapore, 2019; (d) M. Gon, S. Ito, K. Tanaka and Y. Chujo, Design

Strategies and Recent Results for Near-Infrared-Emissive Materials Based on Element-Block π -Conjugated Polymers, *Bull. Chem. Soc. Jpn.*, DOI: 10.1246/bcsj.20210235.

10 For reviews on multi-azides as hub molecules for multi-functional materials, see: (a) D. Fournier, R. Hoogenboom and U. S. Schubert, Clicking Polymers: A Straightforward Approach to Novel Macromolecular Architectures, *Chem. Soc. Rev.*, 2007, **36**, 1369–1380; (b) W. H. Binder and R. Sachsenhofer, ‘Click’ Chemistry in Polymer and Material Science: An Update, *Macromol. Rapid Commun.*, 2008, **29**, 952–981; (c) K. Li, D. Fong, E. Meichsner and A. Adronov, A Survey of Strain-Promoted Azide–Alkyne Cycloaddition in Polymer Chemistry, *Chem. – Eur. J.*, 2021, **27**, 5057–5073. For recent research on multi-azides as energetic materials or as material precursors, see: (d) Y. Wang, Y. Liu, T. Lu, F. Gao and B. Zhao, Synthesis and Properties of 3-Azido-2,2-bis(azidomethyl)propyl 2-Azidoacetate: A Potential Azido Ester Plasticizer, *ChemPlusChem*, 2019, **84**, 107–111; (e) M. Claßen, S. B. Heimsch and T. M. Klapötke, Synthesis and Characterization of New Azido Esters Derived from Malonic Acid, *Propellants, Explos., Pyrotech.*, 2019, **44**, 1515–1520; (f) T. Ikeda and Y. Matsushita, Tetrahedral Tetra-Cationic Ionic Liquids, *Chem. Lett.*, 2020, **49**, 14–16; (g) M. Oba, H. Takazaki, N. Kawabe, M. Doi, Y. Demizu, M. Kurihara, H. Kawakubo, M. Nagano, H. Suemune and M. Tanaka, Helical Peptide-Foldamers Having a Chiral Five-Membered Ring Amino Acid with Two Azido Functional Groups, *J. Org. Chem.*, 2014, **79**, 9125–9140.

11 A.-M. Caminade, R. Laurent, B. Delavaux-Nicota and J. P. Majoral, “Janus” Dendrimers: Syntheses and Properties, *New J. Chem.*, 2012, **36**, 217–226.

12 R. Miyajima, K. Sakai, Y. Otani, T. Wadatsu, Y. Sakata, Y. Nishikawa, M. Tanaka, Y. Yamashita, M. Hayashi, K. Kondo and T. Hayashi, Novel Tetrafunctional Probes Identify Target Receptors and Binding Sites of Small-Molecule Drugs from Living Systems, *ACS Chem. Biol.*, 2020, **15**, 2364–2373.

13 (a) H. Wang and D. J. Mooney, Metabolic Glycan Labelling for Cancer-Targeted Therapy, *Nat. Chem.*, 2020, **12**, 1102–1114; (b) A. I. Ponomarenko, V. A. Brylev, K. A. Sapozhnikova, A. V. Ustinova, I. A. Prokhorenko, T. S. Zatsepina and V. A. Korshun, Tetrahedral DNA Conjugates From Pentaerythritol-based Polyazides, *Tetrahedron*, 2016, **72**, 2386–2391; (c) H. Yang and F. Seela, “Bis–Click” Ligation of DNA: Template–Controlled Assembly, Circularisation and Functionalisation with Bifunctional and Trifunctional Azides, *Chem. – Eur. J.*, 2017, **23**, 3375–3385; (d) R. V. Thaner, I. Eryazici, O. K. Farha, C. A. Mirkina and S. T. Nguyen, Facile one-step solid-phase synthesis of multitopic organic–DNA hybrids via “click” chemistry, *Chem. Sci.*, 2014, **5**, 1091–1096.

14 (a) T. Hosoya, T. Hiramatsu, T. Ikemoto, M. Nakanishi, H. Aoyama, A. Hosoya, T. Iwata, K. Maruyama, M. Endo and M. Suzuki, Novel Bifunctional Probe for Radioisotope-Free Photoaffinity Labeling: Compact Structure Comprised of Photospecific Ligand Ligation and Detectable Tag Anchoring Units, *Org. Biomol. Chem.*, 2004, **2**, 637–641; (b) S. Yoshida, K. Kanno, I. Kii, Y. Misawa, M. Hagiwara and T. Hosoya, Convergent Synthesis of Trifunctional Molecules by Three Sequential Azido-type-selective Cycloadditions, *Chem. Commun.*, 2018, **54**, 3705–3708; (c) M. Belkheira, D. El Abed, J.-M. Pons and C. Bressy, Chemoselective Organoclick–Click Sequence, *Synthesis*, 2018, 4254–4262; (d) S. Yoshida, Y. Sakata, Y. Misawa, T. Morita, T. Kuribara, H. Ito, Y. Koike, I. Kii and T. Hosoya, Assembly of four modules onto a tetraazide platform by consecutive 1,2,3-triazole formations, *Chem. Commun.*, 2021, **57**, 899–902. For recent review, see ref. 6.

15 (a) T. Yokoi, H. Tanimoto, T. Ueda, T. Morimoto and K. Kakiuchi, Site-Selective Conversion of Azido Groups at Carbonyl α -Positions to Diazo Groups in Diazido and Triazido Compounds, *J. Org. Chem.*, 2018, **83**, 12103–12121; (b) T. Yokoi, T. Ueda, H. Tanimoto, T. Morimoto and K. Kakiuchi, Site-Selective Conversion of Azido Groups at Carbonyl α -Positions into Oxime Groups Leading Triazide to Triple Click Conjugation Scaffold, *Chem. Commun.*, 2019, **55**, 1891–1894.

16 Recently, 2-azidoacrylamides have been developed as compact platforms for efficient modular synthesis through selective click reaction. See. (a) S. Ariyasu, H. Hayashi, B. Xing and S. Chiba, Site-Specific Dual Functionalization of Cysteine Residue in Peptides and Proteins with 2-Azidoacrylates, *Bioconjugate Chem.*, 2017, **28**, 897–902; (b) H. Takemura, S. Goto, T. Hosoya and S. Yoshida, 2-Azidoacrylamides as compact platforms for efficient modular synthesis, *Chem. Commun.*, 2020, **56**, 15541–15544.

17 (a) N. Münster, P. Nikodemak and U. Koert, Chemoselective Layer-by-Layer Approach Utilizing Click Reactions with Ethynylcyclooctynes and Diazides, *Org. Lett.*, 2016, **18**, 4296–4299; (b) V. Uдумula, H. S. Nazari, S. R. Burt, M. N. Alfindee and D. J. Michaelis, Chemo- and Site-Selective Alkyl and Aryl Azide Reductions with Heterogeneous Nanoparticle Catalysts, *ACS Catal.*, 2016, **6**, 4423–4427; (c) D. Svatunek, N. Houszka, T. Hamlin, M. Bickelhaupt and H. Mikula, Chemoselectivity of Tertiary Azides in Strain-promoted Alkyne–Azide Cycloadditions, *Chem. – Eur. J.*, 2019, **25**, 754–758.

18 For interesting reaction acceleration by a steric effect, see: (a) S. Yoshida, A. Shiraishi, K. Kanno, T. Matsushita, K. Johmoto, H. Uekusa and T. Hosoya, Enhanced Clickability of Doubly Sterically-hindered Aryl Azides, *Sci. Rep.*, 2011, **1**, 82; (b) S. Yoshida, J. Tanaka, Y. Nishiyama, Y. Hazama, T. Matsushita and T. Hosoya, Further Enhancement of the Clickability of Doubly Sterically-hindered Aryl Azides by para-Amino Substitution, *Chem. Commun.*, 2018, **54**, 13499–13502; (c) S. Yoshida, S. Goto, Y. Nishiyama, Y. Hazama, M. Kondo, T. Matsushita and T. Hosoya, Effect of Resonance on the Clickability of Alkenyl Azides in the Strain-promoted Cycloaddition with Dibenzo-fused Cyclooctynes, *Chem. Lett.*, 2019, **48**, 1038–1041.

19 (a) C. Uttamapinant, A. Tangpeerachaikul, S. Grecian, S. Clarke, U. Singh, P. Slade, K. R. Gee and A. Y. Ting, Fast, Cell-Compatible Click Chemistry with Copper-Chelating Azides for Biomolecular Labeling, *Angew. Chem., Int. Ed.*, 2012, **51**, 5852–5856; (b) Z. Yuan, G.-C. Kuang, R. J. Clark and L. Zhu, Chemoselective Sequential “Click” Ligation Using Unsymmetrical Bisazides, *Org. Lett.*, 2012, **14**, 2590–2593; (c) S. A. Ingale and F. Seela, Stepwise Click Functionalization of DNA through a Bifunctional Azide with a Chelating and a Nonchelating Azido Group, *J. Org. Chem.*, 2013, **78**, 3394–3399; (d) V. Bevilacqua, M. King, M. Chaumontet, M. Nothisen, S. Gabillet, D. Buisson, C. Puente, A. Wagner and F. Taran, Copper-Chelating Azides for Efficient Click Conjugation Reactions in Complex Media, *Angew. Chem., Int. Ed.*, 2014, **53**, 5872–5876; (e) Y. Su, L. Li, H. Wang, X. Wang and Z. Zhang, All-in-one Azides: Empowered Click Reaction for *in vivo* Labeling and Imaging of Biomolecules, *Chem. Commun.*, 2016, **52**, 2185–2188; (f) A. Sallustro, S. Bregant, C. Chollet, D. Audisio and F. Taran, Scalable and Practical Synthesis of Clickable Cu-Chelating Azides, *Chem. Commun.*, 2017, **53**, 7890–7893.

20 For enantioselective discrimination of organic azides, see: (a) J. Meng, V. V. Fokin and M. G. Finn, Kinetic Resolution by Copper-catalyzed Azide-alkyne Cycloaddition, *Tetrahedron Lett.*, 2005, **46**, 4543–4546; (b) E.-C. Liu and J. J. Topczewski, Enantioselective Copper Catalyzed Alkyne-Azide Cycloaddition by Dynamic Kinetic Resolution, *J. Am. Chem. Soc.*, 2019, **141**, 5135–5138; (c) J. R. Alexander, A. A. Ott, E.-C. Liu and J. J. Topczewski, Kinetic Resolution of Cyclic Secondary Azides, Using an Enantioselective Copper-Catalyzed Azide-Alkyne Cycloaddition, *Org. Lett.*, 2019, **21**, 4355–4358; (d) W. D. G. Brittain, A. G. Dalling, Z. Sun, C. S. Le Duff, L. Male, B. R. Buckley and J. S. Fossey, Coetaneous Catalytic Kinetic Resolution of Alkynes and Azides Through Asymmetric Triazole Formation, *Sci. Rep.*, 2019, **9**, 15086; (e) C. Wang, R.-Y. Zhu, K. Liao, F. Zhou and J. Zhou, Enantioselective Cu(I)-Catalyzed Cycloaddition of Prochiral Diazides with Terminal or 1-Iodoalkynes, *Org. Lett.*, 2020, **22**, 1270–1274; (f) E.-C. Liu and J. J. Topczewski, Enantioselective Nickel-Catalyzed Alkyne-Azide Cycloaddition by Dynamic Kinetic Resolution, *J. Am. Chem. Soc.*, 2021, **143**, 5308–5313.

21 (a) J. Dommerholt, O. van Rooijen, A. Borrmann, C. F. Guerra, F. M. Bickelhaupt and F. L. van Delft, Highly Accelerated Inverse Electron-demand Cycloaddition of Electron-deficient Azides with Aliphatic Cyclooctynes, *Nat. Commun.*, 2014, **5**, 5378; (b) S. Xie, S. A. Lopez, O. Ramström, M. Yan and K. N. Houk, 1,3-Dipolar Cycloaddition Reactivities of Perfluorinated Aryl Azides with Enamines and Strained Dipolarophiles, *J. Am. Chem. Soc.*, 2015, **137**, 2958–2966; (c) S. V. Chapyshev, A. V. Chernyak and I. K. Yakushchenko, Chemoselective Staudinger-Phosphite Reaction on the Azido Groups of 2,4,6-Triazido-3,5-dibromopyridine, *J. Heterocycl. Chem.*, 2016, **53**, 970–974; (d) M. Sundhoro, S. Jeon, J. Park, O. Ramström and M. Yan, Perfluoroaryl Azide Staudinger Reaction: A Fast and Bioorthogonal Reaction, *Angew. Chem., Int. Ed.*, 2017, **56**, 12117–12121; (e) T. Meguro, N. Terashima, H. Ito, Y. Koike, I. Kii, S. Yoshida and T. Hosoya, Staudinger Reaction Using 2,6-Dichlorophenyl Azide Derivatives for Robust Aza-ylide Formation Applicable to Bioconjugation in Living Cells, *Chem. Commun.*, 2018, **54**, 7904–7907; (f) N. Terashima, Y. Sakata, T. Meguro, T. Hosoya and S. Yoshida, Triazole Formation of Phosphinyl Alkynes with Azides Through Transient Protection of Phosphine by Copper, *Chem. Commun.*, 2020, **56**, 14003–14006; (g) L. Cheng, X. Kang, D. Wang, Y. Gao, L. Yi and Z. Xi, The One-pot Nonhydrolysis Staudinger Reaction and Staudinger or SPAAC Ligation, *Org. Biomol. Chem.*, 2019, **17**, 5675–5679; (h) X. Kang, X. Cai, L. Yi and Z. Xi, Multifluorinated Aryl Azides for Development of Improved H₂S Probes, and Fast SPAAC and Staudinger Reactions, *Chem. – Asian J.*, 2020, **15**, 1420–1429.

22 (a) T. Meguro, S. Yoshida, K. Igawa, K. Tomooka and T. Hosoya, Transient Protection of Organic Azides from Click Reactions with Alkynes by Phosphazide Formation, *Org. Lett.*, 2018, **20**, 4126–4130; (b) T. Aimi, T. Meguro, A. Kobayashi, T. Hosoya and S. Yoshida, Nucleophilic transformations of azido-containing carbonyl compounds via protection of azido group, *Chem. Commun.*, 2021, **57**, 6062–6065.

23 (a) W. D. Lambert, Y. Fang, S. Mahapatra, Z. Huang, C. W. am Ende and J. M. Fox, Installation of Minimal Tetrazines through Silver-Mediated Liebeskind-Srogl Coupling with Arylboronic Acids, *J. Am. Chem. Soc.*, 2019, **141**, 17068–17074; (b) S. D. Schnell, L. V. Hoff, A. Panchagnula, M. H. H. Wurzenberger, T. M. Klapötke, S. Sieber, A. Linden and K. Gademann, 3-Bromotetrazine: Labelling of Macromolecules via Monosubstituted Bifunctional s-Tetrazines, *Chem. Sci.*, 2020, **11**, 3042–3047; (c) E. Ros, M. Bellido, X. Verdaguer, L. R. de Pouplana and A. Riera, Synthesis and Application of 3-Bromo-1,2,4,5-Tetrazine for Protein Labeling to Trigger Click-to-Release Bioorthogonal Reactions, *Bioconjugate Chem.*, 2020, **31**, 933–938.

24 Y. Tian and Q. Lin, Fitness Factors for Bioorthogonal Chemical Probes, *ACS Chem. Biol.*, 2019, **14**, 2489–2496.

25 Although no example of selective reaction has been shown, direct conversion of alkyl azides to diazo compounds has been reported before our works (ref. 15). See: (a) G. B. Feigelson, On the conversion of azides to diazo-compounds, *Tetrahedron Lett.*, 1998, **39**, 1129–1130; (b) E. L. Myers and R. T. Raines, A Phosphine-Mediated Conversion of Azides into Diazo Compounds, *Angew. Chem., Int. Ed.*, 2009, **48**, 2359–2363; (c) H.-H. Chou and R. T. Raines, Conversion of Azides into Diazo Compounds in Water, *J. Am. Chem. Soc.*, 2013, **135**, 14936–14939.

26 (a) M. Kumasaki, K. Kinbara, Y. Wada, M. Arai and M. Tamura, Azidoacetamide, a Neutral Small Organic Azide, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2001, **57**, 06–08; (b) J. M. Dyke, G. Levita, A. Morris, J. S. Ogden,

A. A. Dias, M. Algarra, J. P. Santos, M. L. Costa, P. Rodrigues and M. T. Barros, Study of the Thermal Decomposition of 2-Azidoacetamide by Ultraviolet Photoelectron Spectroscopy and Matrix-Isolation Infrared Spectroscopy: Identification of the Imine Intermediate $\text{H}_2\text{NCOCHNH}$, *J. Phys. Chem. A*, 2004, **108**, 5299–5307; (c) S. Cecioni, J.-P. Praly, S. E. Matthews, M. Wimmerová, A. Imbert and S. Vidal, Rational Design and Synthesis of Optimized Glycoclusters for Multivalent Lectin-Carbohydrate Interactions: Influence of the Linker Arm, *Chem. – Eur. J.*, 2012, **18**, 6250–6263; (d) N. Collins, R. Connan, G. Sánchez-Sanz and P. Evans, Isomerisation of Vinyl Sulfones for the Stereoselective Synthesis of Vinyl Azides, *Eur. J. Org. Chem.*, 2020, 6228–6235 Very recently, Raines and co-workers also proposed the presence of intramolecular hydrogen bonding in α -AzSAs, which caused a significant difference in the reaction rates of SPAAC reactions with their newly developed cycloalkynes. See. (e) J. M. Dones, N. S. Abularrage, N. Khanal, B. Gold and R. T. Raines, Acceleration of 1,3-Dipolar Cycloadditions by Integration of Strain and Electronic Tuning, *J. Am. Chem. Soc.*, 2021, **143**, 9489–9497.

27 For acidity of N-H in amides, see. (a) F. G. Bordwell, J. A. Harrelson and T. Y. Lynch, Homolytic Bond Dissociation Energies for the Cleavage of α -N-H Bonds in Carboxamides, Sulfonamides, and Their Derivatives. The Question of Synergism in Nitrogen-Centered Radicals, *J. Org. Chem.*, 1990, **55**, 3337–3341; (b) F. G. Bordwell and G. Z. Ji, Effects of Structural Changes on Acidities and Homolytic Bond Dissociation Energies of the Hydrogen-nitrogen Bonds in Amidines, Carboxamides, and Thiocarboxamides, *J. Am. Chem. Soc.*, 1991, **113**, 8398–8401.

28 S. Xie, M. Sundhoro, K. N. Houk and M. Yan, Electrophilic Azides for Materials Synthesis and Chemical Biology, *Acc. Chem. Res.*, 2020, **53**, 937–948.

29 (a) T.-A. Okamura, H. Yamamoto and N. Ueyama, Conformational Switching Between Acids and their Anions by Hydrogen Bonding, in *Hydrogen Bonding and Transfer in the Excited State*, ed. K.-L. Han, G.-J. Zhao, John Wiley & Sons, West Sussex, 2011 For synthetic application using intramolecular bonding with N-H of amides, see: (b) I. A. O’Neil, N. D. Miller, J. Peake, J. V. Barkley, C. N. R. Low and B. Kalindjian, The Novel Use of Proline Derived Amine Oxides in Controlling Amide Conformation, *Synlett*, 1993, 515–517; (c) X. H. Liu, L. L. Lin and X. M. Feng, Chiral N,N'-Dioxides: New Ligands and Organocatalysts for Catalytic Asymmetric Reactions, *Acc. Chem. Res.*, 2011, **44**, 574–587.

30 (a) W. Q. Tian and Y. A. Wang, Mechanisms of Staudinger Reactions within Density Functional Theory, *J. Org. Chem.*, 2004, **69**, 4299–4308; (b) W. Q. Tian and Y. A. Wang, Dynamics of the Staudinger Reaction, *J. Chem. Theory Comput.*, 2005, **1**, 353–362; (c) G. C. Fortman, B. Captain and C. D. Hoff, Thermodynamic Investigations of the Staudinger Reaction of Trialkylphosphines with 1-Adamantyl Azide and the Isolation of an Unusual s-cis Phosphazide, *Inorg. Chem.*, 2009, **48**, 1808–1810; (d) M. W. P. Bebbington and D. Bourissou, Stabilised phosphazides, *Coord. Chem. Rev.*, 2009, **293**, 1248–1261.

31 (a) F. L. Lin, H. M. Hoyt, H. van Halbeek, R. G. Bergman and C. R. Bertozzi, Mechanistic Investigation of the Staudinger Ligation, *J. Am. Chem. Soc.*, 2005, **127**, 2686–2695; (b) M. B. Soellner, B. L. Nilsson and R. T. Raines, Reaction Mechanism and Kinetics of the Traceless Staudinger Ligation, *J. Am. Chem. Soc.*, 2006, **128**, 8820–8828.

32 (a) E. Saxon and C. R. Bertozzi, Cell Surface Engineering by a Modified Staudinger Reaction, *Science*, 2000, **287**, 2007–2010; (b) E. Saxon, S. J. Luchansky, H. C. Hang, C. Yu, S. C. Lee and C. R. Bertozzi, Investigating Cellular Metabolism of Synthetic Azidosugars with the Staudinger Ligation, *J. Am. Chem. Soc.*, 2002, **124**, 14893–14902 For recent reviews, see: (c) Z.-P. A. Wang, C.-L. Tiana and J.-S. Zheng, The Recent Developments and Applications of the Traceless-Staudinger Reaction in Chemical Biology Study, *RSC Adv.*, 2015, **5**, 107192–107199; (d) S. Liu and K. J. Edgar, Staudinger Reactions for Selective Functionalization of Polysaccharides: A Review, *Biomacromolecules*, 2015, **16**, 2556–2571; (e) C. Bednarek, I. Wehl, N. Jung, U. Schepers and S. Bräse, The Staudinger Ligation, *Chem. Rev.*, 2020, **120**, 4301–4354; (f) T. K. Heiss, R. S. Dorn and J. A. Prescher, Bioorthogonal Reactions of Triarylphosphines and Related Analogue, *Chem. Rev.*, 2021, **121**, 6802–6849.

33 (a) H. Zhang, H. Tanimoto, T. Morimoto, Y. Nishiyama and K. Kakiuchi, Regioselective Rapid Synthesis of Fully Substituted 1,2,3-Triazoles Mediated by Propargyl Cations, *Org. Lett.*, 2013, **15**, 5222–5225; (b) H. Zhang, H. Tanimoto, T. Morimoto, Y. Nishiyama and K. Kakiuchi, Acid-mediated Synthesis of Fully Substituted 1,2,3-Triazoles: Multicomponent Coupling Reactions, Mechanistic Study, Synthesis of Serine Hydrolase Inhibitor and its Derivatives, *Tetrahedron*, 2014, **70**, 9828–9835; (c) Y. Zhang, J. Li, M. Wang, H. Zhang, H. Tanimoto, T. Morimoto and K. Kakiuchi, Synthesis of Fused 1,2,3-Triazoles through Carbocation-Mediated Intramolecular [3 + 2] Cycloaddition of Azido-propargyl Alcohols, *Heterocycles*, 2017, **94**, 1775–1782; (d) Y. Zhang, M. Wang, J. Li, Q. Di, Z. Tian, B. Chen, H. Zhang, H. Tanimoto, T. Morimoto and K. Kakiuchi, Acid Promoted Metal Free Synthesis of Triazole-Fused Heterocycles via Intramolecular [3 + 2] Cycloaddition, *Heterocycles*, 2018, **96**, 943–953.

34 Since the wavenumbers of the azido groups in IR absorption hardly change, IR spectra are not suitable to evaluate NH-N₃ interactions. See: E. Lieber, C. N. R. Rao, T. S. Chao and C. W. W. Hoffman, Infrared Spectra of Organic Azides, *Anal. Chem.*, 1957, **29**, 916–918.

35 In Wang’s works, the reactivity against Staudinger reduction was estimated from the chemical shifts of NMR. However, in our case, the tendency against the reaction was not clear. For precedented examples, see. (a) P. T. Nyffeler, C.-H. Liang, K. M. Koeller and C.-H. Wong, The Chemistry

of Amine-Azide Interconversion: Catalytic Diazotransfer and Regioselective Azide Reduction, *J. Am. Chem. Soc.*, 2002, **124**, 10773–10778 For the application of chemical shift indication, see: (b) J. Li, H.-N. Chen, H. Chang, J. Wang and C.-W. T. Chang, Tuning the Regioselectivity of the Staudinger Reaction for the Facile Synthesis of Kanamycin and Neomycin Class Antibiotics with N-1 Modification, *Org. Lett.*, 2005, **7**, 3061–3064; (c) J. Li, F.-I. Chiang, H.-N. Chen and C.-W. T. Chang, Investigation of the Regioselectivity for the Staudinger Reaction and Its Application for the Synthesis of Aminoglycosides with N-1 Modification, *J. Org. Chem.*, 2007, **72**, 4055–4066; (d) Y. Berkov-Zrihen, I. M. Herzog, M. Feldman and M. Fridman, Site-Selective Displacement of Tobramycin Hydroxyls for Preparation of Antimicrobial Cationic Amphiphiles, *Org. Lett.*, 2013, **15**, 6144–6147.

36 For example, see. (a) O. Bakhanovich and P. Beier, Synthesis, Stability and Reactivity of α -Fluorinated Azidoalkanes, *Chem. – Eur. J.*, 2020, **26**, 773–782; (b) M. Mamone, R. S. B. Gonçalves, F. Blanchard, G. Bernadat, S. Ongeri, T. Milcent and B. Crousse, N-Difluoromethyl-triazole, as a constrained scaffold in peptidomimetics, *Chem. Commun.*, 2017, **53**, 5024–5027; (c) J. Engel-Andreasen, I. Wellhöfer, K. Wich and C. A. Olsen, Backbone-Fluorinated 1,2,3-Triazole-Containing Dipeptide Surrogates, *J. Org. Chem.*, 2017, **82**, 11613–11619.

37 O. P. Blahun, A. B. Rozhenko, E. Rusanov, S. Zhersh, A. A. Tolmachev, D. M. Volochnyuk and O. O. Grygorenko, Twisting and Turning the Sulfonamide Bond: A Synthetic, Quantum Chemical, and Crystallographic Study, *J. Org. Chem.*, 2020, **85**, 5288–5299.

38 M. D. Velasco, P. Molina, P. M. Fresneda and M. A. Sanz, Isolation, Reactivity and Intramolecular Trapping of Phosphazide Intermediates in the Staudinger Reaction of Tertiary Phosphines with Azides, *Tetrahedron*, 2000, **56**, 4079–4084.

39 M. Formica, D. Rozsar, G. Su, A. J. M. Farley and D. J. Dixon, Bifunctional Iminophosphorane Superbase Catalysis: Applications in Organic Synthesis, *Acc. Chem. Res.*, 2020, **53**, 2235–2247.

40 (a) See the ESI.† (b) L. Yao, A. Grishaev, G. Cornilescu and A. Bax, The Impact of Hydrogen Bonding on Amide ^1H Chemical Shift Anisotropy Studied by Cross-Correlated Relaxation and Liquid Crystal NMR Spectroscopy, *J. Am. Chem. Soc.*, 2010, **132**, 10866–10875.

41 (a) B. L. Nilsson, L. L. Kiessling and R. T. Raines, Staudinger Ligation: A Peptide from a Thioester and Azide, *Org. Lett.*, 2000, **2**, 1939–1941; (b) E. Saxon, J. I. Armstrong and C. R. Bertozzi, A “Traceless” Staudinger Ligation for the Chemoselective Synthesis of Amide Bonds, *Org. Lett.*, 2000, **2**, 2141–2143; (c) P. B. Kapadnis, E. Hall, M. Ramstedt, W. R. J. D. Galloway, M. Welch and D. R. Spring, Towards quorum-quenching catalytic antibodies, *Chem. Commun.*, 2009, 538–540; (d) H. Itoh, K. Miura, K. Kamiya, T. Yamashita and M. Inoue, Solid-Phase Total Synthesis of Yaku’amide B Enabled by Traceless Staudinger Ligation, *Angew. Chem., Int. Ed.*, 2020, **59**, 4564–4571; (e) C. Kitoun, M. Fonvielle, N. Sakkas, M. Lefresne, F. Djago, Q. B. Remaury, P. Poinot, M. Arthur, M. Etheve-Quelquejeu and L. Iannazzo, Phosphine-Mediated Bioconjugation of the 3'-End of RNA, *Org. Lett.*, 2020, **22**, 8034–8038.

42 (a) J. Dommerholt, F. P. J. T. Rutjes and F. L. van Delft, Strain-Promoted 1,3-Dipolar Cycloaddition of Cycloalkynes and Organic Azides, *Top. Curr. Chem.*, 2016, **374**, 16; (b) E. G. Chupakhin and M. Y. Krasavin, Achievements in the synthesis of cyclooctynes for ring strain-promoted [3 + 2] azide-alkyne cycloaddition, *Chem. Heterocycl. Compd.*, 2018, **54**, 483–501.

43 (a) V. S. Sadu, H. N. Roy, P. Arigala, I.-T. Hwang and K.-I. Lee, Entry to Highly Hindered Chiral β -Amino Triazoles Bearing a gem-Diaryl Group by Azide-alkyne Click Chemistry, *Bull. Korean Chem. Soc.*, 2014, **35**, 1605–1612; (b) V. S. Sadu, S. Sadu, S. Kim, I.-T. Hwang, K.-J. Kong and K.-I. Lee, Influence of steric demand on ruthenium-catalyzed cycloaddition of sterically hindered azides, *RSC Adv.*, 2017, **7**, 3229–3232.

44 Although only one competitive reaction example was examined, Sun and Wang’s group reported NHC-CuAAC with a silylated alkyne, affording a triazole product from α -AzSA selectively. See: Y. Xia, L.-Y. Chen, S. Lv, Z. Sun and B. Wang, Microwave-Assisted or Cu-NHC-Catalyzed Cycloaddition of Azido-Disubstituted Alkynes: Bifurcation of Reaction Pathways, *J. Org. Chem.*, 2014, **79**, 9818–9825.