Conversion of Alkyl Azides to Diazo Compounds and the Azide-Site Selectivity: One-Pot Phosphine-Mediated Transient Protection of Azido Groups and Deprotective Transformation to Diazo Groups

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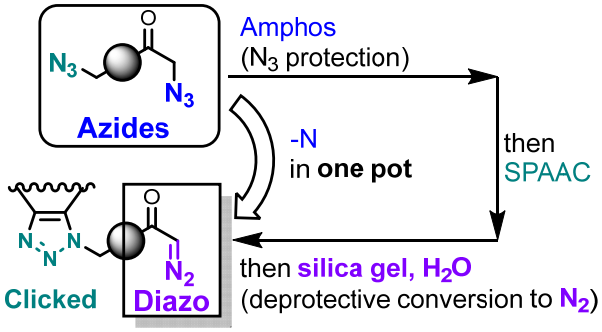
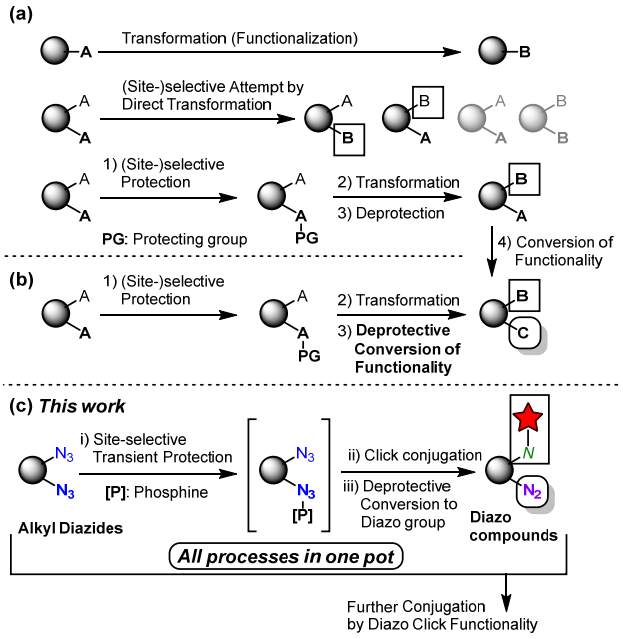


ABSTRACT: A one-pot conversion of alkyl azides to diazo compounds is outlined. After azido group protection of α-azidocarbonyl compounds, treatment of the resulting phosphazides with silica gel in a wet solvent afforded α-diazo carbonyl products by azide-deprotective conversion. Competitive reactions of α-azido amides with alkyl and aryl azides demonstrate azide-site selectivity. Azide-site selective click functionalization by this one-pot sequence is also demonstrated with diazido compounds.

Scheme 1. (Site-)Selective Transformation of Functional Groups for Multiple Functionalization



The transformation or functionalization of molecules is a fundamental and indispensable step in the synthesis of desired compounds. Consequently, there is a constant demand for increased efficiency, shorter steps, and ease of manipulation in molecular synthesis.[1–5] In this regard, the selective transformation of a specific position in the presence of multiple functional groups that are either the same or similarly reactive presents a greater challenge due to the potential generation of multiple by-products as opposed to monofunctionalized compounds (Scheme 1a). For this reason, protection of the appropriate group is often employed to avoid unwanted functionalization.[6] In the case of molecules with the same functional groups, site-selective protection can solve the above problems of synthetic efficiency to suppress side reactions. However, removing the protecting group (deprotection step) only serves to restore the original functional group, and this additional step still does not contribute to synthetic progress.

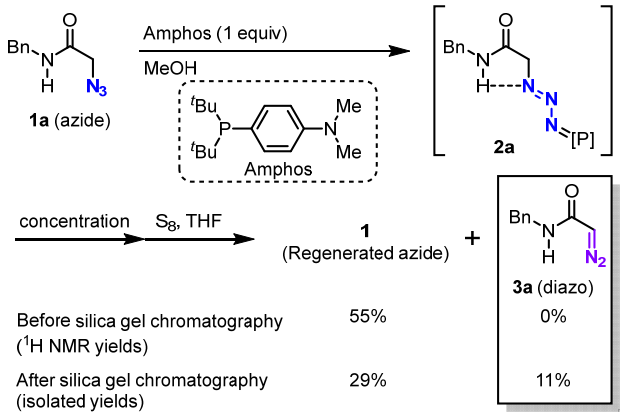
Nevertheless, the protection of functional groups remains important because it is not always possible to achieve an ideal direct (site-)selective transformation or a protecting group-free synthesis.[7,8] Therefore, the development of a deprotection step is worthwhile to improve the efficiency and to contribute to the synthetic progress. For this purpose, deprotective conversion of the protected groups could increase the synthetic efficiency by direct conversion into different functionalities or further contribution to skeletal

construction in one step (Scheme 1b).[9] In line with advancing deprotection through this strategy, we present a novel method for converting azido groups to diazo groups via phosphine-mediated transient protection. With this method, a one-pot sequence was achieved that included site-selective azido protection, click functionalization of unprotected azido groups, and deprotective conversion of the protected azido functionality to the diazo group (Scheme 1c).

Yoshida, Hosoya, and co-workers reported an innovative method for azido group protection.[10–12] Using Amphos, a bulky and electron-rich phosphine, aryl azides were transiently protected as phosphazide structures without dinitrogen elimination via the Staudinger reaction. After click reactions of the unprotected alkyl azide moieties, the aryl azides were restored by treatment with elemental sulfur.

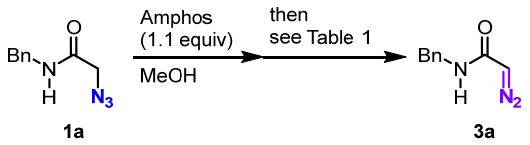
Separately, our group has also explored azide-site-selective reactions to achieve discriminative conjugation of multiple components onto multi-azide scaffolds.[13–15] Based on our recent study of azide site-selective conjugation using intramolecular hydrogen bonding,[15] we addressed the azide protection method for α-azide amide **1a** of alkyl azide (Scheme 2). From ^{1}H NMR in toluene-d8 and HRMS studies (see Figures S1–2), the carbonyl α-position CH_2 remains detectable at this stage. In addition, the remarkable downfield shift observed in the amide N-H signal of phosphazide **2a** suggested an intramolecular interaction between the N-H group and a basic phosphazide nitrogen atom. Unfortunately, the regeneration of the starting azide **1a** (N_3) resulted in only moderate yields. At the same time, however, we observed the unexpected product of the diazo compound **3a** (N_2) after silica gel chromatography.

Scheme 2. Our Discovery of the Azido to Diazo Group Conversion Through Azide Protection.



The diazo group is highly distinctive and has found extensive use in organic chemistry as a carbene precursor for cyclopropanation, C-H/O-H insertion in natural product and polymer synthesis.[16–21] Furthermore, in addition to applications as protein labeling warheads,[22–27] the unique click conjugation reactivity of diazo compounds has been exploited for diazo selective [3+2] cycloadditions in the presence of azides in chemical biology.[28–32] Despite their utility, commonly used methods for introducing diazo groups, such as the diazo transfer method using sulfonyl azides, typically require substrate limitation to 1,3-dicarbonyl structures. In addition to the recent efforts to overcome this limitation in diazo transfer reactions,[33] phosphine or β-elimination-mediated direct conversions of azido (N_3) to diazo (N_2) groups have been developed.[13,34–36] Due to the efficacy of diazo compounds and the demand for functional materials through multicomponent integration,[37] our serendipitous discovery (Scheme 2), which differs significantly from the precedents, inspired us to adopt the strategy of deprotective conversion to diazo groups after azide-site selective transient protection.

Table 1. Optimization of the Diazo Conversion Reaction.



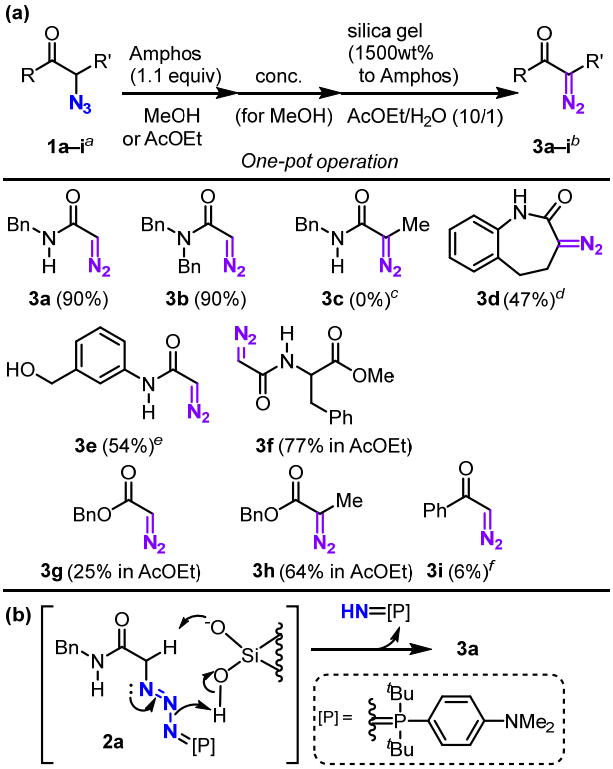
Entry[a]	Conditions	Yield (%)[b]
1	AcOH (2 equiv.)	0
2	$NaHCO_3$ (2 equiv.)	0
3	$Cu(OAc)_2$ (0.1 equiv)	0
4	concentration then silica gel chromatography (hexane/AcOEt elution)	(92)
5	concentration then alumina chromatography (hexane/AcOEt)	(32)
6	Concentration then silica gel (1500wt% to Amphos) in AcOEt/H_2O (10/1)	94 (90) [87 (82)] [c]
7	Deviation from entry 6: no silica gel	0
8	Deviation from entry 6: AcOEt solvent instead of MeOH, and no concentration step	85[d]
9	Deviation from entry 8: toluene solvent	81[e]
10	Deviation from entry 6: Cy_3P instead of Amphos	64
11	Deviation from entry 6: $(Me_2N)_3P$ instead of Amphos	42

[a]0.1 mmol scale. [b]^{1}H NMR yield (isolated yield in bracket). [c]2.0 mmol scale. [d]With recovered **1a** (15%). [e]With recovered **1a** (10%).

We began to evaluate the conditions for the diazo-producing reaction based on the results in Scheme 2 (Table 1). Since the diazo compound **3a** was obtained after silica gel chromatography, we first investigated conditions involving acid[36] and base[34] (entries 1 and 2), but the desired diazo compound **3a** was not observed. The possibility of diazo

formation by oxidation of hydrazones[38] was also excluded (entry 3). Consequently, we returned to the silica gel conditions and chromatography after concentration successfully afforded **3a** in excellent yield (entry 4). However, the elution of **3a** from the silica gel column was markedly slow, regardless of the polarity of the eluting solvents, requiring the use of large volumes of organic solvents. Replacing the silica gel with alumina resulted in a lower yield (entry 5). After several investigations, we hypothesized that the trace amount of water in the eluting solvent or the silica gel slowly generated **3a** during chromatography, and finally established the one-pot sequence conditions of concentration followed by silica gel treatment[38] in wet ethyl acetate (entry 6), which yielded **3a** in a 90% isolated yield. This condition also allowed a similar product yield in a 2.0 mmol scale reaction. The condition with water in the absence of silica gel gave no **3a** (entry 7). Using ethyl acetate or toluene solvent instead of methanol for the azide-protecting step, **3a** was obtained in a similar yield without a concentration step (entries 8, 9). Cy_3P and $(Me_2N)_3P$ could also give **3a** (entries 10, 11), but in lower yields. Other phosphines we have tested did not complete the consumption of **1a**.

Scheme 3. Scope of Substrates and plausible Mechanism

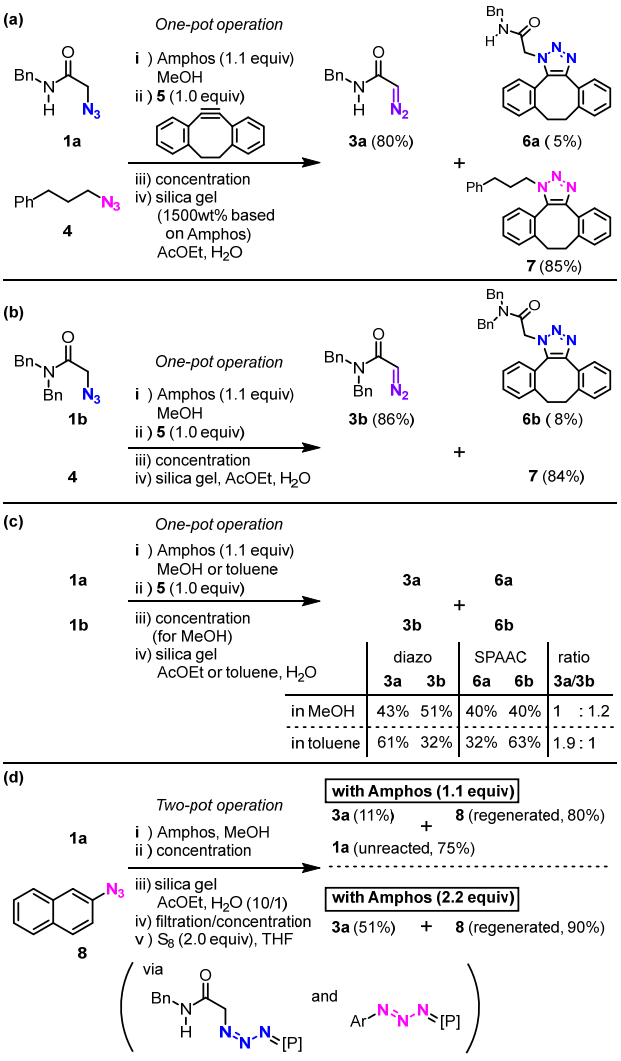


[a]0.1 mmol scale (0.05 mmol scale for **1e**). [b]Isolated yield except for **3i**. [c]Acrylamide was observed in 15% on ^{1}H NMR [d]2.2 equiv of Amphos. [e]1.4 eq of Amphos. [f]With recovered **1i** (44% on ^{1}H NMR).

With the reaction conditions established, the substrate scope of the reaction with monoazides was investigated, yielding isolatable α-diazocarbonyl compounds (Scheme 3a). Not only the secondary amides **1a** to **3a** but also the tertiary amide **1b** were converted to the diazo product **3b** in good yields. Since a trace amount of the corresponding acrylamide was observed, the unsuccessful result of the secondary alkylazide **1c** would be due to the instability of the product under the reaction conditions and the low acidity of the α-hydrogen atom. On the other hand, the lactam substrate **1d** with the secondary alkyl azido group, the hydroxy group-containing **1e** and the Gly-Phe derivative **1f** were successfully delivered to the diazo material. In the case of the esters, the primary alkyl azide was obtained in low yield. Alternatively, the secondary alkyl azide **1h** was improved to give **3h** in moderate yield. However, the ketone **1i** was almost unreactive with Amphos, and the diazo compound **3i** was obtained in only 6%, with 44% recovery of **1e**.

In Cao and Li's recent azide-to-diazo conversion using secondary phosphine oxide and additional acetic acid,[36] the synchronous protonation-deprotonation of the phosphazide oxide intermediates was postulated. It would be plausible that our reaction occurs by a similar mechanism, which could be mediated with the partially hydrolyzed silica gel as a proton source and a base source to extract the carbonyl α-hydrogen atom of **2a** to eliminate the Amphos imide and yield the diazo product (Schemes 3b, S2, S3).

Scheme 4. Competitive Azide Protection-Diazo Conversion Reactions.[a]



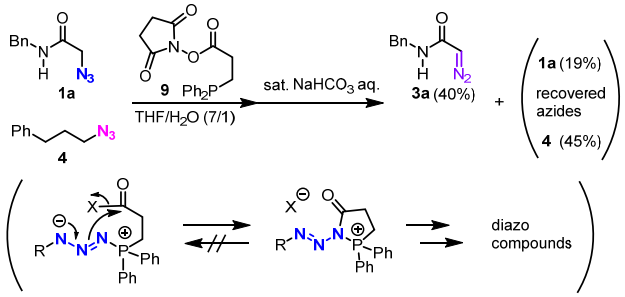
	diazo		SPAAC		ratio
	3a	**3b**	**6a**	**6b**	**3a/3b**
in MeOH	43%	51%	40%	40%	1 : 1.2
in toluene	61%	32%	32%	63%	1.9 : 1

[a] ^{1}H NMR yield.

Next, the azide selectivity was investigated by competitive reactions involving two azido compounds (Scheme 4). The competitive reactions were performed using the following one-pot reaction sequence: (i) azido protection; (ii) SPAAC (strain-promoted azide-alkyne cycloaddition) of the unprotected azido group; (iii) concentration (in the case of methanol solvent); (iv) azide-deprotecive conversion to the diazo group. In the reaction involving secondary amide **1a** and alkyl azide **4** with no carbonyl group, the above reaction sequence afforded diazo compound **3b** from secondary amide **1b** and SPAAC product **7** from general alkyl azide **4** in good yields and with high azide-site selectivity (Scheme 4a). This implies that (i) the azido group of the secondary amide was selectively protected; (ii) SPAAC of the unprotected azide occurred; (iii and iv) the protected azido group of the secondary amide was converted to the diazo group. It is noteworthy that both azide and diazo compounds are known to be reactive in SPAAC, and the transient protection worked effectively. The tertiary amide azide **1b** also showed excellent selectivity and product yields (Scheme 4b). In contrast, no selectivity was observed in methanol solution compared to secondary and tertiary amides (Scheme 4c). To increase the stability of the phosphazide through intramolecular hydrogen bonding, the use of toluene solvent proved to be effective, resulting in the main product **3a** in a 1.9:1 ratio.

Since the reported protection studies were mainly performed with aryl azides,[10–12] we also investigated the azide selectivity with aryl azide (Scheme 4d). After treatments with silica gel followed by elemental sulfur, both azides **8** and **1a** were obtained in good yields, with a minor diazo product **3a** observed, demonstrating aryl azide-selective protection. This observation suggests that the selectivity in azido group masking is strongly influenced by the thermodynamic stability of the adduct phosphazide.[10] Consequently, α-azidocarbonyl compounds are preferentially protected over general alkyl azides and aryl azides over α-azidocarbonyl compounds. Furthermore, this study showed that the decomposition of aryl phosphazides into diazo compounds does not occur under the silica gel conditions established for alkyl azides. Taking advantage of this tolerance of the aryl phosphazide intermediate to silica gel, the use of 2.2 equiv. of Amphos to mask both **1a** and **8** resulted in the diazo compound 3a and the regenerated aryl azide **8**, respectively.

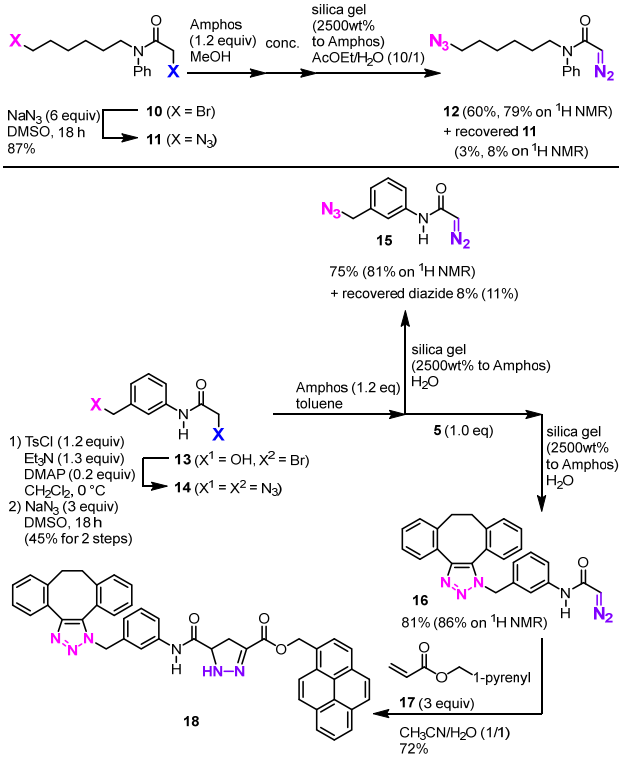
Scheme 5. Competitive Diazo Conversion Reaction by Raines' method[a]



[a] ^{1}H NMR yields.

For comparison with the previously reported azide-to-diazo conversion method, the azide selectivity was investigated using Raines' pioneering method (Scheme 5).[34] As a result, the diazo compound **3a** was obtained, but in 40% yield. In addition, only 45% of **4** was recovered, suggesting the potential production of the unstable diazo compound from **4**. The Staudinger reaction consists of the equilibrium step between the starting azides and the phosphine adducts. However, Raines' method has been proposed to consist of the irreversible step of cyclic intermediate formation, which would be kinetic.[34-36] Given these mechanistic differences, our diazo conversion via the thermodynamic pathway may have improved the azide-site selectivity.

Scheme 6. Azide-site selective Diazo Conversion of Diazido Compounds, and Further functionalization[a]



[a]Isolated yield.

Finally, azide-selective protection/deprotective diazo conversion with diazides was demonstrated by intramolecular competition (Scheme 6). Diazide **11**, composed of alkyl and tertiary amido azides, prepared by the one-step global azidation of **10**, was subjected to diazo conversion. Subsequent azido site-selective conversion was achieved to successfully afford the diazo azido product **12** in moderate isolated yield. In the reports of Hosoya and Yoshida, benzylic azido groups are also protectable.[10] Thus, diazide **14** with benzylic and secondary amido-α-position azido groups is challenging in terms of site selectivity. As a result, carbonyl-α-position selective diazo conversion was achieved to give **15**, and SPAAC by site-selective protection followed by deprotective diazo conversion was demonstrated to give the corresponding SPAAC-coupled diazo product **16** with excellent azido group selectivity. The resulting diazoamide **16** was then successfully coupled with acrylate **17** via a

[3+2] cycloaddition reaction to give the three-component conjugate **18**.[28,31]

In summary, we have developed a new method for the conversion of the alkyl azido group to the diazo group. The one-pot conversion of α-azidocarbonyl compounds to the corresponding diazo products via selective protection and deprotective conversion allowed for azide-site selective application among alkyl azides. The unique nature of our conversion method could improve the direct azide-to-diazo conversion and azide protection/deprotection methods to an azide protection/deprotective diazo conversion sequence. This work will provide a new method for the preparation of diazo compounds and further enable the versatile use of multi-azide scaffolds[39] for multicomponent conjugation to functional materials in polymer science and chemical biology.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the website.

Experimental procedure, characterization data, and NMR spectra (PDF)

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Author Contributions

RA and KT performed the synthetic experiments and collected the analytical data. HT conceptualized this project, checked the collected analytical data, and performed supervision. TT contributed to the discussion on this project. The first draft was written by HT and was updated by all authors.

Notes

The authors declare no competing financial interest.

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