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Neighboring Nitrogen Atom-Induced Reactions of Azidoacetyl Hydrazides, including Unexpected Nitrogen-Nitrogen Bond Cleavage of the Hydrazide

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Abstract: We studied the hydrazide compounds of the α-azidoacetyl group, which showed specific click reactivity by the intramolecular hydrogen bonding between the azido group and the N-H of the hydrazide moiety. In the competitive click reactions with a general alkyl azide, both traceless and non-traceless Staudinger-Bertozzi ligation occurred azide-site-selectively by the acceleration effect of the hydrogen bonding. However, the product obtained from the traceless reaction was further transformed into heterocyclic compounds. In addition, in an attempt at a synthesis of naphthalimide-possessing azidoacetyl hydrazide, nitrogen-nitrogen bond cleavage of the azidoacetyl hydrazides occurred to give the reduced amine product. These unexpected results could help design molecules for the successful Staudinger-Bertozzi ligation of the hydrazide compounds and develop a new nitrogen-nitrogen bond cleavage method.

Keywords: organic azides; staudinger ligation; nitrogen-nitrogen bond cleavage; hydrogen-bonding interaction; click chemistry

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1. Introduction

Click chemistry, which conjugates two molecules concisely, has been utilized in broad scientific areas such as chemical biology and polymer material chemistry [1–4]. Beyond this established one-on-one conjugation chemistry, a strategy integrating multiple functional compounds onto one scaffold molecule has received much attention recently (Figure 1a) [5,6]. Among the multi-click modular hub strategy, organic azides' high reactivity, sufficient stability, and small steric influence to play an important role [7–10]. In addition, the azido group is easily introducible onto the substrate at the late stage of the synthesis, for example, by late-stage global S_N2 azidation. For these reasons, multi-azides, which possess multiple azido groups, have sparked interest in readily preparable click scaffolds of integration.

On the other hand, the drawback of the remaining multi-azides is on the site-selectivity of click conjugation. Significantly, the similar reactivities among alkyl azides create difficulty on site-specificity without the help of steric bulkiness. Nevertheless, the presence of sterically bulky substituents suppresses the click reactivity itself and influences the solubility, as well as the performance, of the materials. To improve the site-specificity, we have studied the multi-azide scaffold strategy, which is free from steric bulkiness-based discrimination (Figure 1b) [11–13]. By utilizing the high acidity of C-H at the carbonyl α-positions, we have established azide-site-selective conversion reactions from azido to diazo and oxime groups for multicomponent click conjugation [11,12]. In addition, we recently developed a new azide-site-selective conjugation strategy utilizing the intramolecular hydrogen bonding interactions between amide N-H [14,15] and the azido groups of α-azido secondary amides (α-AzSAs) [13]. As the hydrogen bonding between amide N-H changes the electron density of the azido group and stabilizes the phosphazide intermediates, electrophilic reactions, such as the Staudinger reaction (ligation) [16–20], were

accelerated. In contrast, the nucleophilic conjugation reaction, using propargyl cations that we developed [21,22], was suppressed. With these methods, multiple compounds were successfully and site-selectively integrated onto the di- and tri-azide click scaffolds.

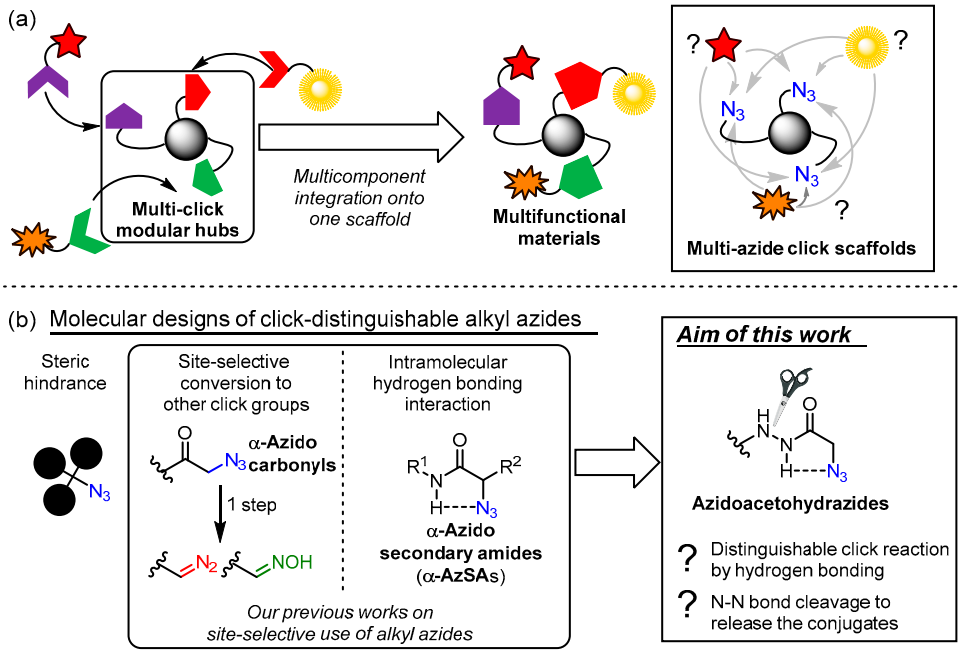
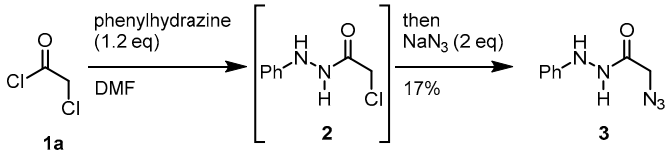


Figure 1. (**a**) Multi-click modular hub strategy (**b**) The designs of distinguishable alkyl azides.

As mentioned above, the reactivity change caused by hydrogen bonding is one of the preferable methods for site-selective click conjugation because it does not require bulky substituents. Thus, to develop the multi-azide scaffold chemistry based on the hydrogen bonding strategy, we next focused on the hydrazides to extend the α-AzSA chemistry [13]. Hydrazides consist of nitrogen-nitrogen bonds in the amide structures, and the bonding can be cleaved under various conditions (reductive conditions in most cases) [23,24]. These chemical bond cleavages could potentially be applied post-removal of the conjugates to release drugs in vivo and remove unnecessary residues after the target protein labeling to reduce contamination for precise analysis [25]. Thus, we envisioned that α-azidoacyl hydrazides could be promising scaffolds, allowing distinguishable click conjugation of multi-azides by intramolecular hydrogen bonding between NH and the azido group and bond cleavage to remove the functions. Herein, we report our attempts at using the azidoacetohydrazides for site-selective click conjugation and the discovered side reaction of the nitrogen-nitrogen bond cleavage of the azidoacetohydrazides.

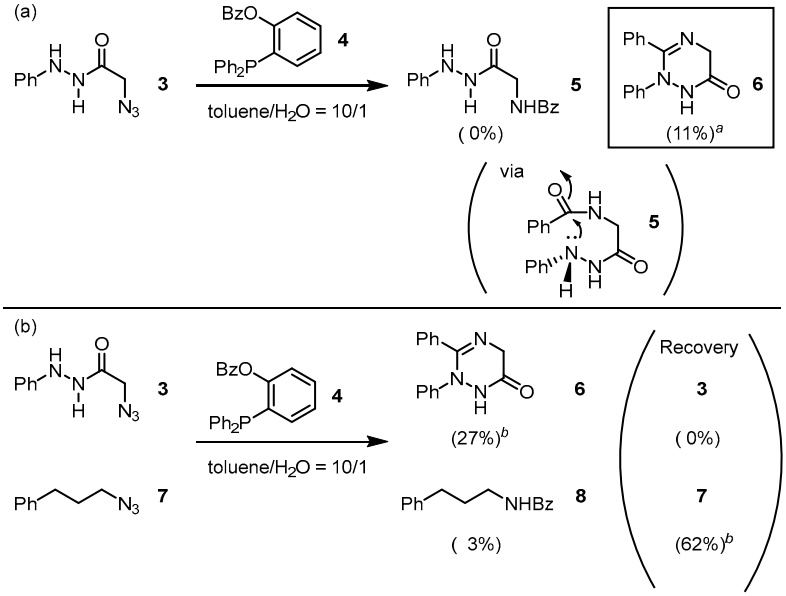
2. Results

First, to examine the characteristics, we commenced our research with the synthesis of the azidoacetohydrazide molecule to be tested. The target compound was synthesized from chloroacetyl chloride **1a**, and chloroacylation of hydrazide followed by S_N2 azidation gave the desired compound **3** in one pot (Scheme 1). Surprisingly, the yield of azidoacetyl hydrazide **3** was quite low, although this precursor **2** was preparable in good yield. Even though the synthesis was performed in two pots ((1) acylation; (2) azidation), the product yield was not improved. In particular, the yield of the azidation step was poor.



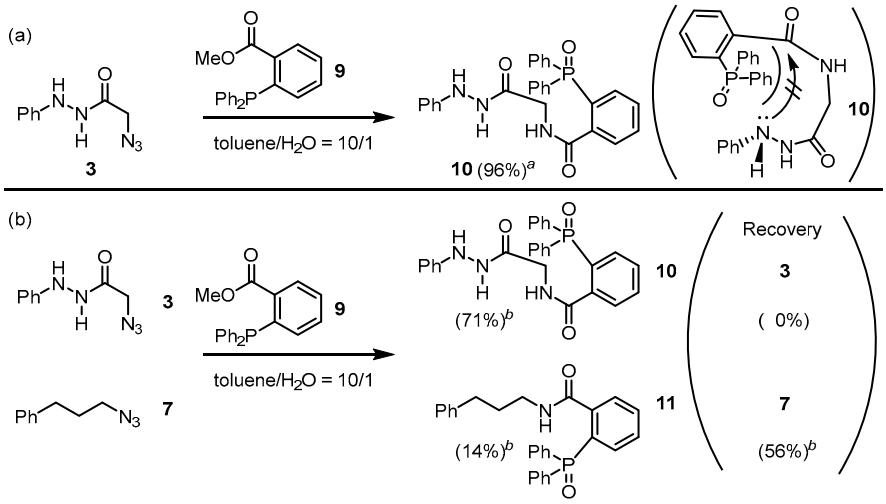
Scheme 1. Synthesis of 2-azido-*N*′-phenylacetohydrazide **3**.

Besides the low yield, with the azidoacetohydrazide **3** in hand, we moved to investigate the traceless Staudinger ligation [26–28]. However, with the phosphine reagent **4**, the desired ligation product benzamide **5** was not obtained, but the cyclized compound 1,2,4-triazin-6-one **6** was, in low yield (Scheme 2a). This slightly unstable compound would be delivered from the desired **5** through the intramolecular condensation with the amine moiety of the hydrazide. In the case of α-AzSA, the intramolecular hydrogen bonding between amide N-H and the azido group increases the reactivity in the Staudinger reaction [13]. The reaction selectivity by the intramolecular hydrogen bonding was also observed in the traceless Staudinger ligation of the azidoacetohydrazide in a competitive reaction. With a general alkyl azide of 3-phenylpropyl azide **7**, the traceless ligation reaction selectively proceeded with **4** showing hydrogen bonding, and **7** was only recovered as an unreacted starting material (Scheme 2b).



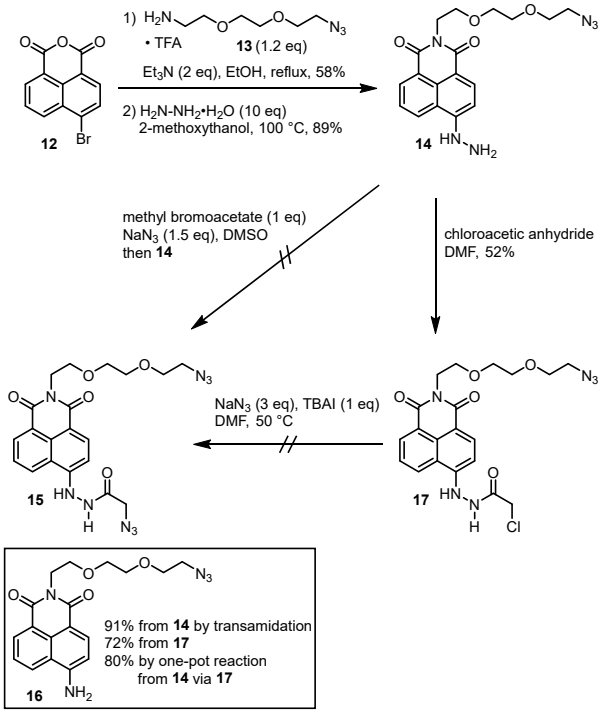
Scheme 2. Traceless Staudinger ligation of azidoacetohydrazide **3**. (**a**) Unexpected cyclization; (**b**) Competitive reaction. [a] Isolated yield. [b] Yields determined by ^{1}H NMR.

To evaluate the reactivity of the azidoacetohydrazide against Staudinger ligation, we also tested the classical non-traceless Staudinger ligation reaction (Staudinger-Bertozzi ligation) [16–20]. In the case of phosphine **9**, ligation product **10** was successfully obtained in an excellent yield without further cyclization (Scheme 3a). Compared to the structural differences between **4** and **9**, the phosphine oxide moiety at the *ortho*-position of benzamide in **10** should prevent the further nucleophilic attack of the amine onto the carbonyl group. Thus, Staudinger ligation successfully afforded the ligation product in contrast to the traceless Staudinger ligation. This result also indicates the difficulty of the traceless Staudinger ligation of acetohydrazides due to the further intramolecular cyclization by the amino nitrogen atoms. With this successful result of non-traceless Staudinger ligation, the competitive ligation reaction using **9** also preferred **3**, which shows a hydrogen interaction in contrast to **7** (Scheme 3b). As a result, ligation product **10** was obtained in moderate selectivity, and **7** was the only recovered starting material.



Scheme 3. Non-traceless Staudinger ligation of azidoacetohydrazide **3**. (**a**) Ligation with phosphine **9**.; (**b**) Competitive reaction. [a] Isolated yield. [b] Yields determined by ^{1}H NMR.

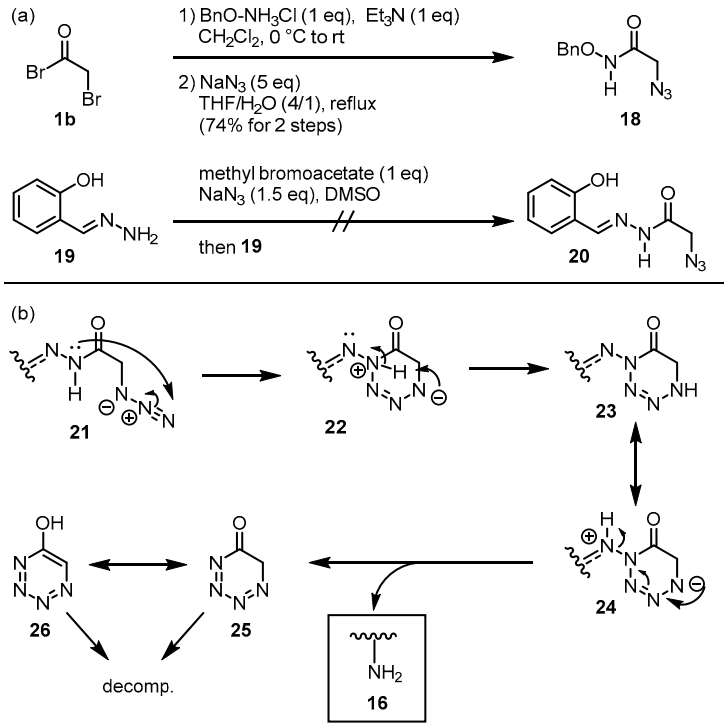
To further research the characteristics of the α-azidoacetyl hydrazides, we moved the synthesis of the model diazide scaffold toward the site-selective click conjugation for the integrated chemical probes (Scheme 4). Starting from the commercially available **12**, imidation with alkylazido tether **13,** followed by S_NAr hydrazination, gave **14** in good yields. With **14**, the one-pot construction of azidoacetyl hydrazide moiety in the diazide scaffold **15** by transamidation [29] was examined with the in situ prepared methyl azidoacetate, at room temperature. However, hydrazide **15** was not obtained. Instead, nitrogen-nitrogen bond-cleaved amine **16** was obtained in a high yield. To investigate this phenomenon, we detoured through the synthesis of chloroacetyl hydrazide **17**. In contrast to phenyl compound **2**, the azidation reaction of **17** did not proceed at room temperature. After heating, amine **16** was obtained in a good yield, the same as the transamidation route. These results suggest that the structure of azidoacetyl hydrazide itself would be unstable.



Scheme 4. N-N bond cleavage on the preparation attempt of α-azidoacetyl hydrazide-consisted diazide click scaffold.

3. Discussion

Because of the insolubility of the aryl position derivatives of **3**, it was difficult to examine and compare the reactivity. For this reason, to compare the stability, we synthesized azidoacetyl hydroxamate **18**. Although **18** also has an electron-rich oxygen atom, **18** was successfully obtained in good yield as a stable compound (Scheme 5a). In contrast, the synthetic approach from hydrazone **19** [30], which could produce azicoacetohydrazone **20**, did not work due to the similar decomposition through bond cleavage. This result indicates that the α-effect of the neighboring nitrogen atom, which increases the nucleophilicity of the amide nitrogen atoms [31,32], plays a key role rather than its basicity. With these results, the plausible N-N bond cleavage mechanism of azidoacetohydrazide **15** to give amine **16** is shown in Scheme 5b. As a result of the α-effect of the nitrogen atom moiety, which could be stronger than that of the oxygen atom [33], intramolecular cyclization of the amido nitrogen to the terminal nitrogen atom of the azido group would occur to form six-membered ring heterocycle **23,** or **24** through **22**. Then, the ammonium moiety of **24** would be eliminated to afford the obtained amine **16**. At the same time, 1,2,3,4-tetrazin-5(6*H*)-one **25** or 1,2,3,4-tetrazin-5-ol **26** of its tautomer, which has not been reported yet, could also be generated and might be unstable enough to decompose quickly. As aminoacetyl hydrazides have been reported to have been obtained in good to excellent yields [34], bond cleavage by Lossen rearrangement [35], which the electron-donating group at carbonyl α-position accelerates, could be excluded from the possible mechanism.



Scheme 5. (**a**) Comparison of preparation of hydroxamate and acylhydrazone of azidoacetamides.; (**b**) Plausible mechanism of nitrogen-nitrogen bond cleavage of hydrazide **15** to give amine **16** and the potentially associated product.

This phenomenon could be a reason for the low yield of phenyl hydrazide **3**. The base-promoted cyclization to tetrazines has been reported with alkyl azides and azaoxyallyl cations from α-bromo hydroxamates in the fluorous solvent [36], particularly hexafluoroisopropyl alcohol (HFIP), providing specific reactivity [37,38]. However, as demonstrated in Scheme 5a, the reported cyclization or the possible bond scission did not occur in the hydroxamate in a non-fluorous general solvent. In contrast, with the hydrazides, the nitrogen-nitrogen bond cleavage proceeded even in a non-fluorous solvent. It should be

noted that the general α-azido secondary or tertiary amides we have examined previously did not show this decomposition reaction [11–13]. The α-Azido secondary or tertiary amides were obtained in excellent yields and were stable enough to handle. As the nucleophilicity of the amide nitrogen is increased due to the neighboring electron-donative amino group [30,31], the α-azidoacetohydrazide molecules would allow this reaction.

Organic azides have also been known for carbon-carbon bond migrative cleavage [7–10,39]. The conversion reaction we found could be worth developing as a new aspect of organic azides for the nitrogen-nitrogen bond cleavage method at ambient temperatures, under non-reductive or non-oxidative reaction conditions. However, the possible generation of **25/26**, a potentially detonation-possible low molecular weight compound with a low Smith ratio (C+O)/n = 0.75), possessing four continuous nitrogen atoms, is also suggested and should be approached with care.

4. Conclusions

In summary, we studied the hydrazide compounds of the α-azidoacetyl group, showing the specific click reactivity by the intramolecular hydrogen bonding. In the competitive reactions, with 3-phenylpropyl azide of a general alkyl azide, both Staudinger and traceless Staudinger ligation resulted in selective ligation by the acceleration effect of the hydrogen bonding. However, the product obtained from the traceless reaction was further transformed into heterocyclic compounds, causing a low yield. In addition, the naphthalimide-possessing azidoacetyl hydrazide decomposed through nitrogen-nitrogen bond cleavage to give the amine product. These results could help to realize the issue of Staudinger ligation of the α-azidoacyl hydrazide compounds and provide its solution for successful ligation. In addition, the bond cleavage of α-azidoacyl hydrazide could give a new nitrogen-nitrogen bond cleavage method under simple amidation conditions or by stepwise amidation/azidation sequence. However, at the same time, the potential generation of the possibly hazardous side product of unstable tetrazine in this reaction is also plausible. We hope our report can help design the azido click scaffold, develop new chemical bond scission methods, and avoid unexpected potential hazards.

5. Materials and Methods

5.1. General Information including Important Notices

Caution!: Organic azides, especially multiple azido compounds, are potentially hazardous and explosive. Although we have never experienced severe incidents in our study, all manipulations of them should be carefully conducted, in a hood with a glass shield, to avoid a detonation. Sodium azide should be handled with a plastic spatula. At the azidation stages, the complete removal of residual halogenated solvent used in the last step or extractions should be kept in mind. Otherwise, explosive species such as diazidomethane from dichloromethane are possibly generated [40,41]. Furthermore, as well as considering Smith's ratio (special attention be paid to the compounds of (C+O)/n < 3)), organic azides should be designed and prepared with due consideration of their structure, stability, and the reactivity of azido groups [42]. Particularly in this paper, we reported the potential generation of possibly hazardous 1,2,3,4-tetrazin-5 (6*H*)-one **25** or its tautomer **26**. Therefore, the running scale of the nitrogen-nitrogen bond cleavage reaction should be small enough and conducted with care.

Analysis and Reagents: The ^{1}H and ^{13}C NMR spectra were recorded using a JEOL JNM-ECX400P/TIM spectrometer (400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR, and 202 MHz for ^{31}P NMR). Chemical shifts are reported as δ values in ppm and calibrated with respect to the residual solvent peak ($CDCl_3$: δ 7.26 for ^{1}H NMR, and δ 77.00 for ^{13}C NMR; Acetone-d_6: δ 2.05 for ^{1}H NMR and δ 29.24 for ^{13}C NMR), internal standard reagent (tetramethylsilane: δ 0.0 for ^{1}H NMR), and external standard reagent (Phosphoric acid: δ 0.00 for ^{31}P NMR). The abbreviations used are as follows: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), and m (multiplet). The NMR spectra of the compounds are shown in Supplementary Material. The melting points were measured using an As

One melting point apparatus DTM-02. The infrared spectra were measured using a JASCO FT/IR-460Plus spectrometer. The mass spectra were recorded using a Thermo Scientific LTQ Orbitrap XL ETD (ESI-Orbitrap). The progress of the reactions was monitored by silica gel thin layer chromatography (TLC) (Merck TLC Silica gel 60 F_{254}). Phosphomolybdic acid ethanol solution, ninhydrin, or iodine on silica gel was used for the TLC stains, and TLC was also monitored with UV lamp (254 or 365 nm). Flash column chromatography was performed using neutral silica gel N60 from Kanto Chemical Co. Inc. or Chromatorex PSQ 100 B from Fuji Silicia as neutral silica gel was used for column chromatography. All of the reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd., TCI (Tokyo Chemical Industry, Co. Ltd., Tokyo, Japan), Kanto Chemical Co. Inc., Kishida chemical, and Nacalai Tescque. Anhydrous solvents such as tetrahydrofuran (THF), toluene, and dichloromethane were purchased from Wako Pure Chemical and Kanto Chemical. Deionized water was used for solvents, reaction quenching, and separation sequences.

5.2. Synthesis of Substrates

2-Azido-*N*-phenylacetohydrazide (**3**) (Figure 2)

Chloroacetyl chloride (318 µL, 4 mmol) was added to a stirred solution of phenylhydrazine (472 µL, 4.8 mmol) in DMF (2 mL), at ambient temperature. After 25 min, sodium azide (780 mg, 12 mmol) was added to the mixture and was kept stirred at the same temperature. After 24 h, diethyl ether and water were added to the mixture to extract the material. The organic layer was washed with water and brine, then dried over sodium sulfate. The removal of the solvent under reduced pressure followed by silica gel column chromatography (hexane/ethyl acetate = 4/1) gave **3** (84 mg, 11%).

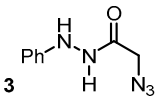


Figure 2. 2-Azido-*N*-phenylacetohydrazide (**3**).

Orange oil; R_f value 0.35 (hexane/ethyl acetate = 1/1); IR (NaCl, $CHCl_3$) ν_{max} 2115, 1702, 1604, 1383 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) observed as two conformational isomers: δ 8.33 (s, 1H, major), 7.67 (s, 1H, minor), 7.20–7.25 (m, 2H), 6.91 (t, 1H, *J* = 7.3 Hz), 6.77 (d, 2H, *J* = 7.3 Hz, major), 6.66 (d, 2H, *J* = 7.8 Hz, minor), 6.24 (s, 1H, major), 5.81 (s, 1H, minor), 4.01 (s, 2H, minor), 3.97 (s, 2H, major); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1 (minor), 167.1 (major), 147.1 (major), 146.4 (minor), 129.5 (minor), 129.2 (major), 121.7 (minor), 121.5 (major), 113.5 (major), 112.7 (minor), 51.4 (major), 49.5 (minor); HRMS (ESI) calcd for $C_8H_9N_5NaO$ $[M+Na]^+$ 214.0705, found 214.0695.

3-Phenylpropyl azide (**7**) (Figure 3)

The compound was prepared by following our previous reports [13,39].

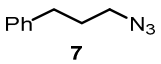


Figure 3. 3-Phenylpropyl azide (**7**).

2-(Diphenylphosphaneyl)phenyl benzoate (**4**) (Figure 4)

Triethylamine (307 µL, 2.2 mmol) and benzoyl chloride (256 µL, 2.2 mmol) were added to a stirred solution of (2-hydroxyphenyl)diphenylphosphine (556 mg, 2 mmol) in dichloromethane (20 mL) at room temperature, successively. After 2 h, the organic components were extracted with ethyl acetate, and the organic layer was washed with water, 5 wt% sodium bicarbonate aqueous solution, and brine. The organic layer was dried over sodium sulfate. The removal of the solvent under reduced pressure, followed by silica gel column chromatography (hexane/ethyl acetate = 50/1), gave the product **4** (631 mg, 83%).

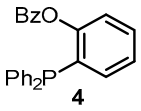


Figure 4. 2-(Diphenylphosphaneyl)phenyl benzoate (**4**).

White solid; R_f value 0.24 (hexane/ethyl acetate = 30/1); m.p. 91.1–93.0 °C; IR (NaCl, $CHCl_3$) ν_{max} 3019, 1520, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, 2H, *J* = 8.6, 1.2 Hz), 7.53 (m, 1H), 7.42 (ddd, 1H, *J* = 7.6, 7.4, 0.8 Hz), 7.37–7.28 (m, 13H), 7.18 (t, 1H, *J* = 7.2 Hz), 6.85 (ddd, 1H, *J* = 7.4, 4.4, 1.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 152.7, 135.4, 134.0, 133.4, 130.7, 130.1, 129.9, 129.1, 129.0, 128.6, 128.5, 128.2, 126.1, 122.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ -14.9; HRMS (ESI) calcd for $C_{25}H_{19}O_2P$ $[M+H]^+$ 383.1201, found 383.1198.

Methyl 2-(diphenylphosphaneyl)benzoate (**9**) (Figure 5)

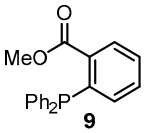


Figure 5. Methyl 2-(diphenylphosphaneyl)benzoate (**9**).

The compound was prepared by following the reported procedure [13].

2,3-Diphenyl-1,2-dihydro-1,2,4-triazin-6(5*H*)-one (**6**) (Figure 6)

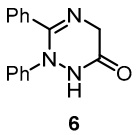


Figure 6. 2,3-Diphenyl-1,2-dihydro-1,2,4-triazin-6(5*H*)-one (**6**).

2-(diphenylphosphino)phenyl benzoate **4** (122 mg, 0.32 mmol) was added to a stirred solution of azidoacetylhydrazide **3** (55.3 mg, 0.29 mmol) in toluene/water(2.9 mL/290 μL = 10/1) at ambient temperature. After two hours, the solvent of the mixture was removed under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1) to give **6** (8.6 mg, 11%). As a result of the product instability, further purification was not performed.

Red oil; R_f value 0.22 (hexane/ethyl acetate = 1/1); IR (NaCl, $CHCl_3$) ν_{max} 1603, 1471, 1382, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, 2H, *J* = 8.5, 1.1 Hz), 7.51 (m, 1H), 7.40 (t, 2H, *J* = 8.0 Hz), 7.23–7.28 (m, 2H), 6.97 (t, 1H, *J* = 7.2 Hz), 6.77 (dd, 2H, *J* = 8.0, 0.8 Hz), 6.41 (brs, 1H), 4.39 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 163.5, 145.6, 131.7, 129.6, 128.5, 128.3, 128.1, 122.3, 113.6, 56.4; HRMS (ESI) calcd for $C_{15}H_{14}N_3O$ $[M+H]^+$ 252.1137, found 252.1131.

2-(Diphenylphosphoryl)-*N*-(2-oxo-2-(2-phenylhydrazinyl)ethyl)benzamide (**10**) (Figure 7)

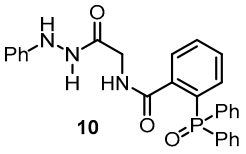


Figure 7. 2-(Diphenylphosphoryl)-*N*-(2-oxo-2-(2-phenylhydrazinyl)ethyl)benzamide (**10**).

Methyl 2-(diphenylphosphino)benzoate **9** (28 mg, 0.087 mmol) was added to a stirred solution of azidoacetyl hydrazide **3** (15.1 mg, 0.079 mmol) in toluene/water (790 μL/79 μL = 10/1) at ambient temperature. After 1.5 h, the solvent of the reaction mixture was removed under reduced pressure. The obtained residue was purified by silica gel

column chromatography (hexane/ethyl acetate = 1/10 to ethyl acetate elution) to give **10** (35.6 mg, 96%).

Beige oil; R_f value 0.14 (hexane/ethyl acetate = 1/10); IR (NaCl, $CHCl_3$) ν_{max} 1674, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.70 (dd, 1H, *J* = 6.8, 2.8 Hz), 7.53–7.63 (m, 7H), 7.41–7.45 (m, 5H), 7.08–7.16 (m, 3H), 6.81–6.86 (m, 3H), 4.04 (d, 2H, *J* = 6.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 168.8, 148.2, 141.1, 133.5, 132.5, 131.9, 131.7, 130.6, 129.7, 129.6, 129.4, 128.8, 128.7, 120.6, 114.0, 43.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 36.6; HRMS (ESI) calcd for $C_{27}H_{25}N_3O_3P$ $[M+H]^+$ 470.1634, found 470.1641.

2-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)-6-bromo-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**14′**) (Figure 8)

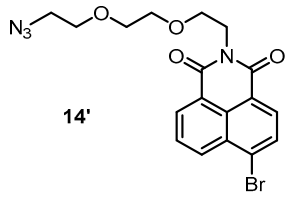


Figure 8. 2-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)-6-bromo-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**14′**).

Commercially available 4-bromo-1,8-naphthalic anhydride **12** (728 mg, 2.63 mmol) and triethylamine (729 μL, 5.26 mmol) was added to a stirred solution of the prepared 2-(2-(2-azidoethoxy)ethoxy)ethanamine **13** [43,44] (908 mg, 3.15 mmol) in ethanol (26 mL) at room temperature. The mixture was heated under reflux conditions for 6 h. Then, additional triethylamine (729 μL, 5.26 mmol) was added to the mixture and was heated for one hour. The solvent was removed under reduced pressure, and the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3.5/1 to 2/1) to obtain **14′** (664 mg, 58%).

White solid; R_f value 0.16 (hexane/ethyl acetate = 4/1); m.p. 215.0–217.2 °C; IR (NaCl, $CHCl_3$) ν_{max} 2106, 1703, 1662, 1370 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, 1H, *J* = 7.2, 0.8 Hz), 8.55 (dd, 1H, *J* = 8.4, 0.8 Hz), 8.39 (d, 1H, *J* = 7.8 Hz), 8.02 (d, 1H, *J* = 7.8 Hz), 7.83 (dd, 1H, *J* = 8.4, 7.2 Hz), 4.43 (t, 2H, *J* = 6.2 Hz), 3.84 (t, 2H, *J* = 6.2 Hz), 3.70–3.72 (m, 2H), 3.60–3.64 (m, 4H), 3.29 (t, 2H, *J* = 5.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.58, 163.56, 133.3, 132.0, 131.2, 131.0, 130.5, 130.3, 129.0, 128.0, 123.0, 122.1, 70.7, 70.2, 69.9, 67.9, 50.6, 39.2; HRMS (ESI) calcd for $C_{18}H_{18}{}^{79}BrN_4O_4$ $[M(^{79}Br)+H]^+$ 433.0511, found 433.0521.

2-(2-(2-(2-azidoethoxy)ethoxy)ethyl)-6-hydrazinyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**14**) (Figure 9)

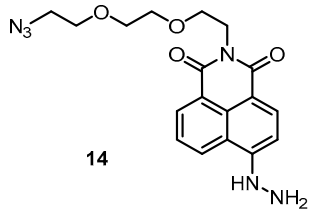


Figure 9. 2-(2-(2-(2-azidoethoxy)ethoxy)ethyl)-6-hydrazinyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**14**).

Hydrazine monohydrate (744 μL, 1.53 mmol) was added to a stirred solution of bromonaphthalimide **14′** (664 mg, 1.53 mmol) in 2-methoxy ethanol (15 mL) at ambient temperature. The mixture was then heated at 100 °C for 17 h. After the reaction mixture was cooled, dichloromethane and water were added to extract the materials, and the organic layer was washed with water and brine. The combined organic layer was dried over sodium sulfate. Removing the solvent under reduced pressure gave the product **14** (513 mg, 87%) in pure form without further purification.

Orange solid; R_f value 0.24 (ethyl acetate only); m.p. 110.0–112.0 °C; IR (NaCl, $CHCl_3$) ν_{max} 2107, 1685, 1647, 1585, 1387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, 1H, *J* = 7.3 Hz),

8.23 (d, 1H, *J* = 8.2 Hz), 7.88 (d, 1H, *J* = 8.2 Hz), 7.35 (dd, 1H, *J* = 7.8, 7.8 Hz), 7.06 (br, 1H), 7.04 (d, 1H, *J* = 8.8 Hz), 4.43 (t, 2H, *J* = 5.5 Hz), 3.96 (t, 2H, *J* = 5.7 Hz), 3.82 (m, 2H), 3.72 (m, 2H), 3.62 (t, 2H, *J* = 5.0 Hz), 3.27 (t, 2H, *J* = 5.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 164.1, 151.8, 134.2, 130.8, 129.0, 125.8, 124.5, 122.2, 118.5, 110.4, 104.5, 70.6, 70.3, 69.8, 68.7, 50.6, 39.0; HRMS (ESI) calcd for $C_{18}H_{21}N_6O_4$ $[M+H]^+$ 385.1624, found 385.1638.

N′-(2-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-chloroacetohydrazide (**17**) (Figure 10)

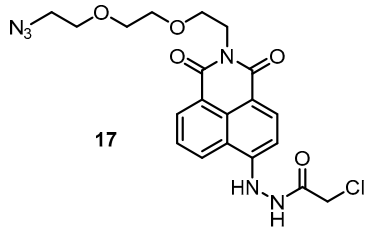


Figure 10. *N*′-(2-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-chloroacetohydrazide (**17**).

Chloroacetic anhydride (27.6 mg, 0.162 mmol) was added to a stirred solution of hydrazine **14** (51.7 mg, 0.134 mmol) in DMF (2 mL) at room temperature. After 3 h, the mixture was treated with diethyl ether and water to extract the material. The organic layer was washed with water and brine and dried over sodium sulfate. The removal of the solvent under reduced pressure, followed by silica gel column chromatography (hexane/ethyl acetate = 1/1 to 1/2 to ethyl acetate elution), gave **17** (32.1 mg, 52%).

Orange oil; R_f value 0.57 (ethyl acetate only); IR (NaCl, acetone) ν_{max} 3392, 3019, 2110, 1694, 1242, 1171, 1036 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.91 (s, 1H), 8.92 (s, 1H), 8.47 (d, 1H, *J* = 8.2 Hz), 8.39 (d, 1H, *J* = 7.3 Hz), 8.32 (d, 1H, *J* = 8.7 Hz), 7.55 (dd, 1 H, *J* = 8.0, 8.0 Hz), 7.12 (d, 1H, *J* = 8.0 Hz), 4.38 (s, 2H), 4.32 (t, 2H, *J* = 6.4 Hz), 3.76 (t, 2H, *J* = 6.6 Hz), 3.68–3.60 (m, 6H), 3.30 (t, 2H, *J* = 4.8 Hz); ^{13}C NMR (101 MHz, acetone-d_6) δ 167.5, 164.6, 164.1, 150.6, 133.9, 131.4, 130.0, 127.9, 126.1, 123.5, 120.4, 113.9, 106.4, 71.09, 71.05, 70.07, 68.4, 51.3, 41.9, 39.5; HRMS (ESI) calcd for $C_{20}H_{22}{}^{35}ClN_6O_5$ $[M(^{35}Cl)+H]^+$ 461.1340, found 461.1354.

6-Amino-(2-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**16**) (Figure 11)

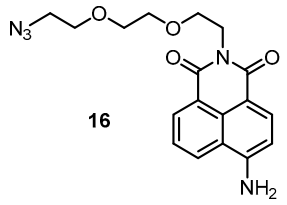


Figure 11. 6-Amino-(2-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**16**).

Orange viscous oil; R_f value 0.62 (ethyl acetate only); IR (NaCl, acetone) ν_{max} 2111, 1655, 1381, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, 1H, *J* = 7.6, 0.8 Hz), 8.41 (d, 1H, *J* = 7.6 Hz), 8.10 (dd, 1H, *J* = 8.4, 0.8 Hz), 7.66 (dd, 1H, *J* = 8.4, 8.0 Hz), 6.76 (d, 1H, *J* = 8.0 Hz), 4.92 (br-s, 1H), 4.43 (t, 2H, *J* = 6.4 Hz), 3.83 (t, 2H, *J* = 6.4 Hz), 3.71 (m, 2H), 3.65–3.60 (m, 5H), 3.28 (t, 2H, *J* = 5.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 164.0, 149.3, 133.8, 131.5, 129.7, 126.9, 124.8, 122.8, 119.8, 109.4, 107.7, 70.6, 70.2, 69.9, 68.3, 50.6, 38.9; HRMS (ESI) calcd for $C_{18}H_{20}N_5O_4$ $[M+H]^+$ 370.1515, found 370.1513.

16 from hydrazine **14** by transamidation

Sodium azide (3.9 mg, 0.06 mmol) was added to a stirred solution of methyl bromoacetate (3.7 μL, 0.04 mmol) in DMSO (400 μL) at ambient temperature. After three hours, hydrazine **14** (15 mg, 0.04 mmol) was added to the mixture. After 13 h, the mixture was

treated with diethyl ether and water to extract the material. The organic layer was washed with water and brine and dried over sodium sulfate. The removal of the solvent under reduced pressure followed by silica gel column chromatography (hexane/ethyl acetate = 1/3) to obtain **16** (13.5 mg, 91%).

16 from chloroacetohydrazide **17**

Sodium azide (4 mg, 0.06 mmol) and tetrabutylammonium iodide (7 mg, 0.02 mmol) were added to a stirred solution of chloroacetohydrazide **17** (8.5 mg, 0.018 mmol) in DMF (300 µL) at ambient temperature. Then, the mixture was heated at 50 °C. After 18 h, the mixture was treated with diethyl ether and water to extract the material. The organic layer was washed with water and brine and dried over sodium sulfate. The removal of the solvent under reduced pressure followed by silica gel column chromatography (hexane/ethyl acetate = 1/1 to 1/2) to obtain **16** (6.1 mg, 72%).

16 from hydrazine **14** via **17** in one pot

Chloroacetic anhydride (10 mg, 0.047 mmol) was added to a stirred solution of hydrazine **14** (15 mg, 0.039 mmol) in DMF (400 µL at ambient temperature. After four hours, sodium azide (15.6 mg, 0.24 mmol) was added, and the mixture was heated at 50 °C. After 20 h, the mixture was treated with diethyl ether and water to extract the material. The organic layer was washed with water and brine and was dried over sodium sulfate. The removal of the solvent under reduced pressure was followed by silica gel column chromatography (hexane/ethyl acetate = 1/1 to 1/2) to obtain **16** (11.6 mg, 80%). Due to the pertial decomposition during the purification, further purification was not performed.

2-Azido-*N*-(benzyloxy)acetamide (**18**) (Figure 12)

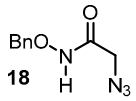


Figure 12. 2-Azido-*N*-(benzyloxy)acetamide (**18**).

Triethylamine (277 µL, 2 mmol) and bromoacetyl bromide **1 b** (174 µL, 2 mmol) were added to a stirred solution of *O*-benzylhydroxylamine hydrochloride (0.32 g, 2 mmol) in dichloromethane (8 mL) at 0 °C, successively. After 25 min, the mixture was warmed up to room temperature. After a further 4.5 h, the mixture was treated with 1 N HCl and brine, and the organic layer was dried over sodium sulfate. The obtained crude material, after the removal of the organic solvent *in vacuo*, was submitted to the next reaction.

Sodium azide (650 mg, 10 mmol) was added to a stirred solution of the crude material in tetrahydrofuran (8 mL) and water (2 mL) at room temperature. Then, the mixture was heated under reflux conditions. After 20 h, the reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water and brine. The washed organic layer was dried over sodium sulfate. Removal of the organic solvent followed by silica gel column chromatography (hexane/ethyl acetate = 1/2) gave the product **18** (304 mg, 74%) as a white solid.

White solid; R_f value 0.38 (hexane/ethyl acetate = 1/1); m.p. 41.0–42.9 °C; IR (NaCl, $CHCl_3$) ν_{max} 2114, 1704, 1473 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (brs, NH), 7.40 (m, 5H), 4.94 (s, 2H), 3.95 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1, 134.6, 129.3, 129.0, 128.7, 78.5, 51.2; HRMS (ESI) calcd for $C_9H_{10}N_4NaO_2$ $[M+Na]^+$ 229.0702, found 229.0700.

2-(Hydrazineylidenemethyl)phenol (**19**) (Figure 13)

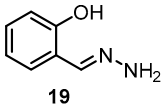


Figure 13. 2-(Hydrazineylidenemethyl)phenol (**19**).

19 was prepared from salicylaldehyde in accordance with the reported procedure [45].

5.3. Competitive Staudinger and Traceless Staudinger Ligation Methods

Traceless Staudinger ligation

Phosphine **4** (38.2 mg, 0.1 mmol) was added to a stirred solution of 2-azido-*N*-phenylacetohydrazide **3** (19.1 mg, 0.1 mmol) and 3-phenylpropyl azide **7** (16.1 mg, 0.1 mmol) in toluene (1 mL) and water (100 µL) at room temperature. After completion of the reaction (4 h), the reaction mixture was concentrated *in vacuo*. The obtained crude mixture was analyzed by ^{1}H NMR with 1,1,2,2-tetrachloroethane (10.5 µL, 0.1 mmol, 5.94 ppm on ^{1}H NMR, 2H) as the internal standard to determine the yields.

NMR yields: Products (**6**: 27%, **8**: 3%) and recovered azides (**3**: 0%, **7**: 62%)

Used peaks to measure NMR yields: **6**: 4.35 ppm (s, 2H), **8**: 3.44 ppm (q, 2H), **3**: 3.52 ppm (q, 2H), **7**: 1.91 ppm (tt, 2H). ^{1}H NMR spectrum of **8** was referred to as that of the reported data [46].

Non-traceless Staudinger ligation

Phosphine **9** (27.2 mg, 0.085 mmol) was added to a stirred solution of 2-azido-*N*-phenylacetohydrazide **3** (16.2 mg, 0.085 mmol) and 3-phenylpropyl azide **7** (13.6 mg, 0.085 mmol) in toluene (1.7 mL) and water (170 µL) at room temperature. After completion of the reaction (2 h), the reaction mixture was concentrated *in vacuo.* The obtained crude mixture was analyzed by ^{1}H NMR with 1,1,2,2-tetrachloroethane (8.9 µL, 0.085 mmol, 5.94 ppm on ^{1}H NMR, 2H) as the internal standard to determine the yields.

NMR yields: Products (**10**: 71%, **11**: 14%) and recovered azides (**3**: 0%, **7**: 58%)

Used peaks to measure ^{1}H NMR yields: **10**: 4.04 ppm (d, 2H), **11**: 2.55 ppm (t, 2H), **3**: 3.52 ppm (q, 2H), **7**: 2.71 ppm (t, 2H). ^{1}H NMR spectrum of **11** was referred to as that in our previous report [13].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/org3040035/s1, for NMR spectra of isolated compounds.

Author Contributions: R.A. and A.O. performed the synthetic experiments and collected the analytical data. H.T. conceptualized this project, checked the collected analytical data, and performed supervision with H.T. and T.T. H.T. and T.T. contributed to the discussion on this project. The first draft was written by H.T. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available in the article and the Supporting Materials.

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Conflicts of Interest: The authors declare no conflict of interest.

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