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Site-Selective Conversion of Azido Groups at Carbonyl α-Positions to Diazo Groups in Diazido and Triazido Compounds

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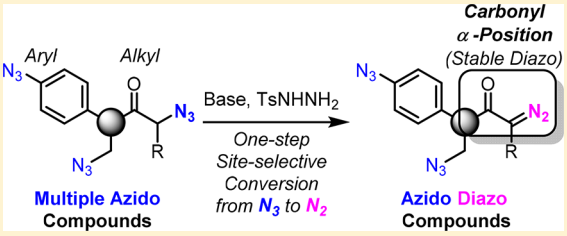
Supporting Information

ABSTRACT: This paper reports on the selective conversion of alkyl azido groups at the carbonyl α-position to diazo compounds. Through β-elimination of dinitrogen, followed by hydrazone formation/decomposition, α-azidocarbonyl moieties were transformed into α-diazo carbonyl groups in one step. As these reaction conditions do not involve aryl or general alkyl azides, site-selective conversions of di- and triazides were achieved. Through this method, the successive site-selective conjugation of the triazido molecule with three different components is demonstrated.



INTRODUCTION

Organic azides (R-N_3) have long been identified as versatile and valuable compounds for the synthesis of natural products, pharmaceuticals, and functional heterocycles.[1] However, despite their widespread application as nitrene precursors and masked amines, recent organic azides have received focus mostly in the optimization of click chemistry by azide−alkyne [3+2] cycloaddition reactions that result in robust conjugations between two molecules.[2] Owing to the synthetic accessibility of the substrates, the azido functional group is still within the main stream of click chemistry.

Given that one-on-one conjugation is now well-established, advancement in this field is aimed toward the site- or chemoselective conjugation of molecules containing multiple clickable groups for versatile functionalization. To date, site-selective conjugation strategies using heterocycles and polyalkyne compounds have been developed.[3−5] In contrast, difficulties remain with compounds containing multiple azido groups (multiple azido compounds) in site-selective reactions, especially among alkyl azido moieties (Scheme 1a).[6] Since multiple azido compounds are easily accessible,[1a,b,e] such as by late-stage global S_N2 azidation, and have a high reactivity with a sufficient molecular stability, they offer promising platforms[7] toward the development of multifunctional element-block materials,[8] such as advanced imaging probes and high-performance polymers, by the integration of various functional units.[2e] Hence, the recent growth of interest in the site-selective manipulations of multiple azido groups in one molecule, such as conjugation,[7,9,10] reduction,[11] protection,[12] and desymmetrization reactions,[13] demands further exploration.

In contrast, despite its structural similarity to the azido (N_3) group, the nature of the diazo (N_2) group is distinctly characteristic.[14] As well as its application as a carbene precursor for cyclopropanation and C−H insertion in natural products and polymer synthesis,[15,16] the diazo functional group exhibits unique click conjugation reactivity to chemoselectively promote [3+2] cycloaddition in the presence of azides and has been developed for application in chemical biology.[17,18] However, the methods of introducing diazo groups often face substrate limitation problems, such as in diazo transfer methods that usually require 1,3-dicarbonyl structures.[14] Owing to its efficiency in synthetic organic chemistry, accessibility to the diazo group should be improved, and the conversion of easily introducible azido groups[1a,b,e] into diazo functions is a solution for this. Recently, the direct transformation of azido into diazo groups has been developed through the Staudinger reaction-based strategy.[19] The application of this strategy to multiple azido compounds could, however, involve undesirable azido positions, such as aryl and nonallylic/benzylic/α-carbonyl alkyl azides,[11,12] which would generate unstable diazo species. To overcome these issues, we herein report a new method that allows the azido group at the carbonyl α-position to selectively transform into a "stable" diazo group (Scheme 1b).

RESULTS AND DISCUSSION

Among the aryl, alkyl, and carbonyl α-positioned azides, we anticipated that the azido group at the carbonyl α-position could be selectively transformed into a diazo group. Through β-elimination using appropriate basic reagents to produce α-imino carbonyl structures followed by in situ condensation with sulfonyl hydrazide to generate the corresponding hydrazones, the same basic conditions could promote the decomposition of sulfonyl hydrazones[1,20] to produce a stable α-diazo carbonyl moiety in one step. Considering the stability of hydrazones, in situ generated ammonia or ammonium salts would not promote reverse reactions. Under these conditions, aryl and alkyl azides without reactive hydrogen atoms should not

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Scheme 1. Multiple Azido/Diazo Compounds

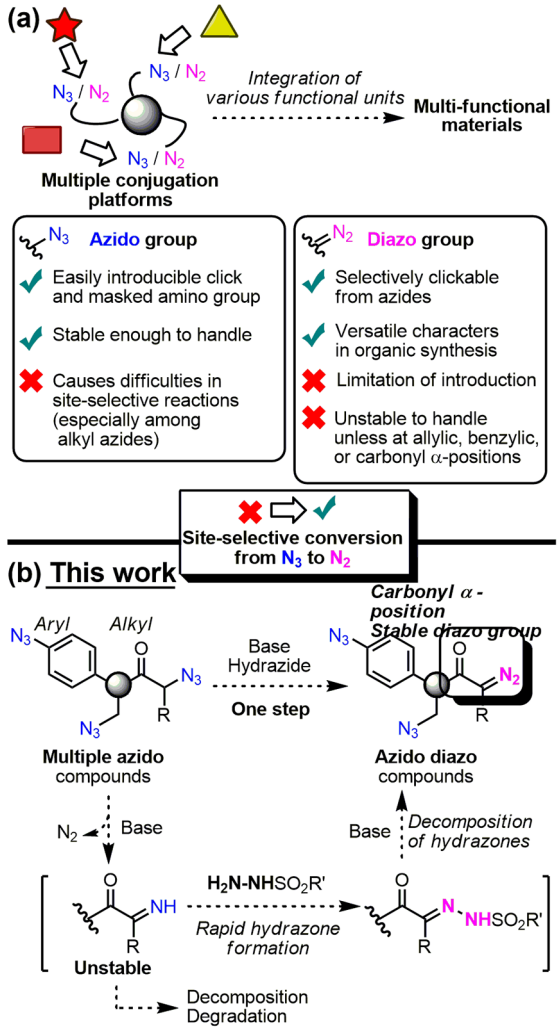
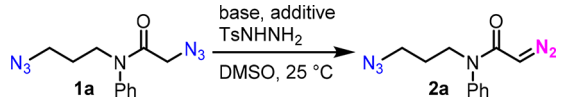
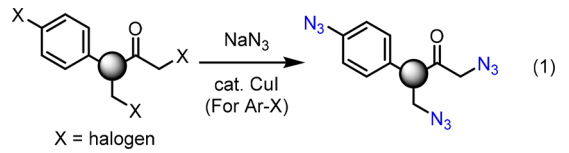


Table 1. Screening of Site-Selective Conversion Conditions from Diazido to Azido Diazo Amide



entry	conditions[a]	yield (%)[b]
1	DBU (5.0 equiv), 48 h	0[d]
2	^{t}BuOK (2.5 equiv), 1 h	56
3	TBAF (5.0 equiv), 2 h	58
4	TBAF (5.0 equiv), H_2O (1 equiv), 2 h	59
5	TBAF (5.0 equiv), $^i Pr_2NEt$ (5.0 equiv), 1 h	71
6	TBAF (5.0 equiv), piperidine (5.0 equiv), 1 h	71
7	TBAF (5.0 equiv), pyrrolidine (5.0 equiv), 1 h	77
8[c]	TBAF (3.6 equiv), pyrrolidine (5.0 equiv), 1 h	84 (90)[d]
9	TBAF (5.0 equiv), K_2CO_3 (2.0 equiv), 2 h	66
10	^{t}BuOK (2.5 equiv), pyrrolidine (2.0 equiv), 1 h	48
11	KF (5.0 equiv), 18-crown-6 (5.0 equiv), CH_3CN, 2 h	0[e]
12	pyrrolidine (5.0 equiv), 6 h	0[e]
13	entry 8 in THF, 24 h	0[f]
14	entry 8 in toluene, 24 h	0[f]
15	entry 7 in ethanol, 24 h	0[e]
16	entry 7 in DMF, 6 h	55
17	entry 8 with 2,4,6-triisopropylbenzenesulfonylhydrazide	0
18	entry 8 with 2,4,6-trimethylbenzenesulfonylhydrazide	28
19	entry 8 with 4-methoxybenzenesulfonylhydrazide	71
20	entry 8 with 2-nitrobenzenesulfonylhydrazide	0

[a]0.1 mmol of **1a**, 0.1 M in DMSO. [b]Isolated yield. [c]0.2 M in DMSO. [d]1.0 mmol scale reaction. [e]No reaction. [f]Obtained in trace amounts.



be damaged. Although elimination of dinitrogen from unactivated alkyl azides by alkoxides of a strong base to obtain the corresponding imines has also been reported,[21] use of appropriate base reagents that can abstract only acidic α-hydrogen of carbonyl groups to promote β-elimination could retain an unactivated alkyl azido position. Moreover, carbonyl α-position-selective transformation is essential to avoid the generation of undesired unstable diazo moiety such as unfunctionalized alkyl diazo groups (Scheme 1a). However, the assumed α-imino carbonyl intermediates, especially those that are unsubstituted, have been reported to be unstable or highly reactive, triggering degradation or polymerization that limit their synthetic applications.[22] Thus, rapid formation of sulfonyl hydrazones before degradation or polymerization should be a key to success.[23] With this background, the polar and aprotic DMSO was selected as a solvent for the immediate condensation of unstable imino carbonyl intermediates at an ambient temperature avoiding potential thermal decomposition of the products (Table 1).

Our investigations began with diazido compound **1a**, which possesses two different alkyl azido groups. To demonstrate the advantageous character of the azido group, all multiple azido substrates we tested were concisely prepared by global azidation of the appropriate halogenated precursors (reaction 1, see Experimental Section). The reaction was first attempted with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, entry 1), but only a trace amount of the product was observed. The use of alkoxides successfully generated 56% of the desired azido diazo compound **2a** (entry 2). For the second step, the reaction should be conducted with weaker bases because alkoxides have been reported to destroy benzylic azides.[21] Among them, TBAF (tetrabutylammonium fluoride) as a base reagent[24] was observed to generate a similar yield to entry 2 (entry 3). Additional water to examine the possible pathway through aldehydes by hydrolysis did not improve the result (entry 4). Probably because of the instability of imino carbonyl intermediates as reported,[22] no hydrolysis product or other isolable side product was obtained. Although further improvement was not accomplished using a single base, we found that applying additional weak bases improved the product yields (entries 5−10). After an extensive survey of organic and inorganic base additives and their amounts, we found that pyrrolidine generated the best and most reproducible yield of 84% and was applicable in large-scale reactions (entry 8). Combination of pyrrolidine with alkoxide (entry 10) resulted in a lower yield than that in entry 2. The fluoride ion from potassium fluoride in the presence of crown ether did not convert the starting azide (entry 11). Because the old bottle of TBAF, which may be partially decomposed, gave **2a** with slightly low and irreproducible yields, TBAF itself would work as a suitable base to extract the α-hydrogen of azidoamides

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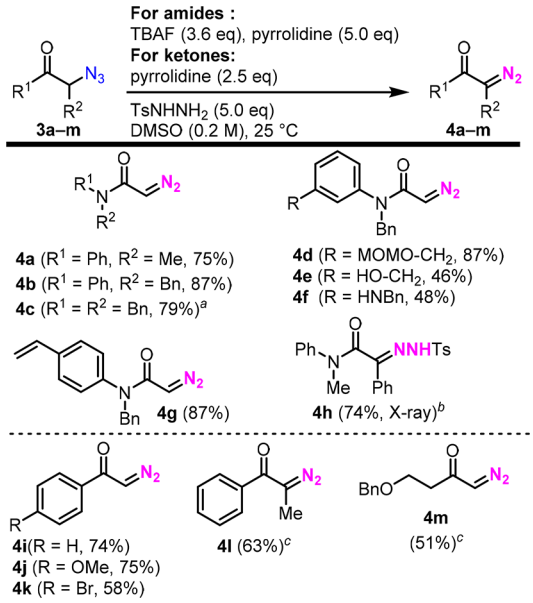
(see Experimental Section). As pyrrolidine itself had no effect in the case of amide as it is not basic enough (entry 12), the efficiency of pyrrolidine or other amines would be at the level of the decomposition of sulfonyl hydrazones.[20e] Due to the instability of α-imino carbonyl intermediates,[22] successive addition of pyrrolidine after consumption of starting materials by TBAF was not efficient. Amines and inorganic base[25] without TBAF required heating and long reaction times (60−80 °C around 30 h) to eliminate dinitrogen and exhibited with low reproducibility. The use of other solvents such as THF, toluene, or ethanol did not yield the desired products, and polar DMF slowly afforded **2a** in a moderate yield (entries 13−16). Additionally, we tested some other sulfonyl hydrazides (entries 17−20). While *p*-methoxyphenylsulfonyl hydrazide gave **2a** in a similar yield (71%), other reactive hydrazides, such as reactive mesityl-, 2-nitrophenyl, or triisopropylphenylsulfonylhydrazides, did not generate satisfactory results owing to their prior decomposition under these conditions before the formation of hydrazones.[20d,f]

After identifying suitable conditions (entry 8 in Table 1), we then scoped the monoazido compounds for general utility of this method (Scheme 2). The substituents on amido-nitrogen atoms

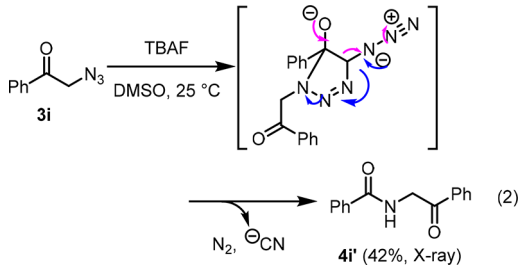
Scheme 2. Scope of Monoazido Substrates



[a]4.4 equiv of TBAF. [b]Without pyrrolidine. [c]0.1 M in DMSO.

(aryl and alkyl) did not influence the conversion to afford **4a−c** in 75%, 87%, and 79% yields, respectively. As well as protected compound **4d**, the substrates **3e−f** bearing hydroxyl and amino groups were also acceptable to this method. As well as the purification stage,[26] inhibition of condensation with hydrazide and imine intermediates by reactive hydroxyl or amino groups might be the reason for their moderate yields. Although the use of sulfonyl hydrazides under basic conditions possibly reduces vinyl groups, **4g** was successfully obtained in 87% yield.[20d] The plausible reaction intermediate sulfonyl hydrazone (Scheme 1b) was confirmed by **4h** (74%) and was stable enough under basic conditions because of the stability of the hydrazone anion by the presence of a phenyl group.

Next, we studied the reaction with ketones. However, the TBAF/pyrrolidine system only produced moderate or low yields of the desired diazo products. Considering that the α-hydrogen of ketones is more acidic than that of amides, we found that sufficient transformation to generate α-diazo ketones was achieved enough using only pyrrolidine of a weak base without TBAF.[26] This result indicates that TBAF for amides is required only to extract α-hydrogen atoms in less acidic compounds. In the case of ketones that produce more stable enolates than amides, we observed a dimerized product such as **4i′** in the absence of aza nucleophiles probably through the [3+2] reaction as depicted in reaction 2.[27] This kind of the side reaction might



also be one of the reasons of moderate yields compared to those of amides. α-Azido acetophenone **3i**, previously converted into **4i** in 49% yield,[19b] and *para*-substituted compounds **3j−k** were efficiently transformed into **4i−k** in 74%, 75%, and 58% yields, respectively. The secondary alkyl azido group in ketone **3l** could produce a similar yield of **4l** (63%). Despite the potential β-elimination, dialkyl ketone **3m** was successfully transformed into diazo product **4m** in 51% yield.

With the successful results from monoazido amides and ketones, we further expanded the scope of the substrates to di- and triazido compounds for site-specific conversion into stable functional diazo groups (Scheme 3). All azido groups in the substrates as well as **1a** were introduced in one step that demonstrated their easy accessibility. Similar to **1a** in Table 1, diazide **1b**, containing azido aryl and α-azido amido moieties, transformed into azido diazo product **2b** in 82% yield. Even in the presence of potentially reactive benzylic azide,[21] **2c** was gratifyingly obtained in 89% yield. We then studied selective diazo formation with substrates possessing two α-azido carbonyl structures. With the appropriate conditions for ketones, diazide **1d** possessing keto- and amido-azido moieties was successfully converted into **2d**. Furthermore, diazo compound **2e** was selectively synthesized from bis(α-azidoamido) material **1e** since the less active secondary alkyl azido amido moiety (less acidic hydrogen) in **1e** remained under the reaction conditions.[26] The moderate yield is probably due to the lability of the α-iminocarbonyl intermediate of this compound since the side product α-azido propionamide without acetyl moiety was obtained as an inseparable mixture. However, the possible inverse azido diazo or bis-diazo products were not observed, and **2e** was obtained as a sole azido diazo product. Subsequently, we submitted triazido substrates, and the azido group at the α-carbonyl position in **5a** with one aryl and two alkyl azido moieties was successfully manipulated to produce diazo molecule **6a**, which possessed distinguishable aryl and alkyl azido groups,[6,9] as a sole product. Furthermore, with tris(alkyl azido) compound **5b** containing keto- and amido-azido fragments, the established reaction conditions with pyrrolidine afforded the diazido keto-diazo product **6b**. The moderate yield of **6b** is following those of monoazido ketones (Scheme 2), and the use of a weak base converted the site-selective keto-azido group in the presence of other two azido groups.

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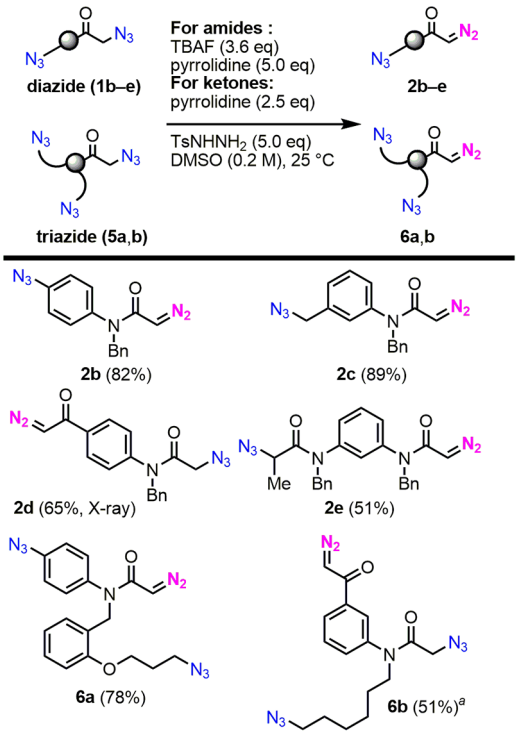
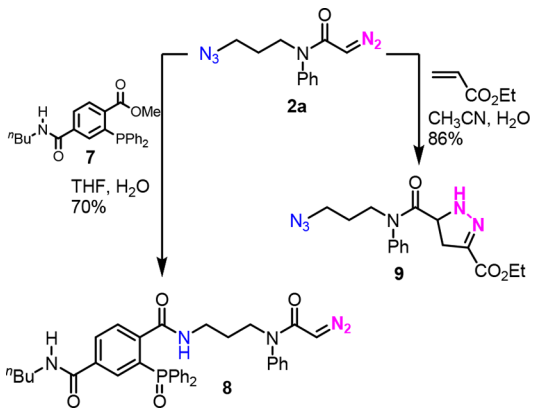
Scheme 3. Site-Selective Conversion to Diazo Groups with Di- and Triazido Compounds



[a]0.1 M in DMSO.

The obtained azido diazo materials are highly versatile,[28] and **2a** was chemoselectively conjugated, as shown in Scheme 4.

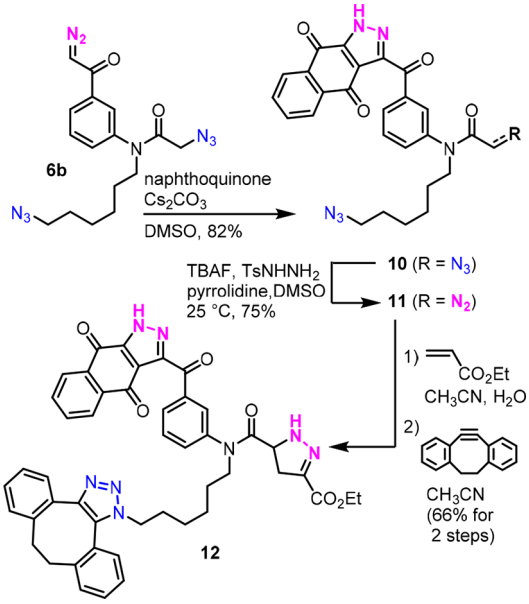
Scheme 4. Chemoselective Conjugation of Azido Diazo Compound



Staudinger–Bertozzi ligation[19b,29] with phosphine **7** produced azido-selectively conjugated diazo compound **8**. On the other hand, diazo-selective conjugation was conducted by [3+2] cycloaddition with acrylate to generate pyrazoline azide **9** as a single isomer.[17]

Finally, we demonstrated the efficiency of our method by site-selective conjugation[7c] of the tris(alkylazido) platform compound **5b** with three different components by the way of successive diazo conversion (Scheme 5). With the generation of diazido diazo compound **6b** from **5b** by ketone-selective conversion (Scheme 3), diazo-selective cycloaddition with naphthoquinone and subsequent air oxidation[25] occurred to afford **10** in

Scheme 5. Successive Conjugation with Three Different Components



82% yield. After the second conversion of the azido group on the amido moiety in **10** to diazo amide **11** in 75% yield, the second diazo-selective [3+2] cyclization with ethyl acrylate,[17] followed by azide-strained alkyne cyclization,[2a,d] successfully furnished **12**. It should be mentioned that each of the three alkyl azido groups in **5b**, which were previously difficult to differentiate,[7] was conjugated with three different dipolarophiles by successive site-selective conversion into diazo groups.

CONCLUSION

In summary, we have achieved the site-selective conversion of azido groups at carbonyl α-positions to diazo groups in one step. As this transformation is dependent on a high reactivity at carbonyl α-positions, aryl and unreactive alkyl azides were not included. With this method, site-selective diazo transformation with the di- and triazido molecules was achieved, as well as the successive integration of various components. This selective azido-manipulation method will likely expand the efficiency and availability of diazo groups and will also develop the site-selective assembly of multiple functional components onto one molecular platform possessing over three types of azido groups. Further development of this site-selective conversion strategy to other clickable groups and application aimed at integration of multiple functional components will be reported in due course.

EXPERIMENTAL SECTION

Caution! Organic azides, especially multiple azido compounds as well as diazo compounds, are potentially hazardous and explosive. Although we have never experienced such an explosion with those used in this study, all manipulations should be carefully conducted behind a safety shield in a hood. Sodium azide should be handled with a plastic spatula. At the azidation stage of azido compound preparation, complete removal of residual halogenated solvent used in the last steps or extractions should be kept in mind to avoid generation of an explosive species such as diazidomethane from dichloromethane.[30]

General Information of Analysis and Reagents. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz for ^{1}H NMR, 126 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) or

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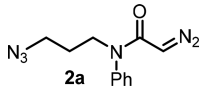
tetramethylsilane (δ 0 for ^{1}H NMR). ^{31}P NMR spectra were calibrated with an external reference (phosphoric acid in benzene-d_6 as δ 0.0). The abbreviations used are as follows: s (singlet), d (doublet), t (triplet), q (quartet), br (broad peak), and m (complex multiplet). Mass spectra were recorded by an EI-magnetic sector (70 eV), CI-magnetic sector, ESI-TOF, and MALDI-spiral TOF. The materials, which were hard to be purified by neutral silica gel column chromatography, were purified by a recycling preparative gel permeation chromatography (GPC; chloroform as an eluent). Dimethyl sulfoxide (DMSO) was distilled under reduced pressure after refluxing in the presence of calcium hydride.

Synthesis of Diazo Compounds. *General Procedure. Storage of TBAF.* Tetrabutylammonium fluoride (TBAF) was purchased as a 1 mol/L solution of THF. Because we encountered irreproducible results when we used old solution, probably due to the decomposition of TBAF by the reagent itself or contaminated water from moisture,[31] the newly purchased bottle of TBAF solution was repacked in small subsection vial bottles. These were filled with nitrogen gas and were stored in the refrigerator. With these small batch bottles, we successfully obtained reproducible results as described in the article. In addition, the use of commercial solid TBAF hydrate or the removal of THF from the reagent solution prior to use gave low yields or irreproducible results. Short path silica gel column chromatography can afford the desired products in good yields. Exposure to the silica gel column for a long time reduced the product yields.

From Amides. TBAF (3.6 equiv, 1.0 M in THF, see also General Information of Analysis and Reagents) was added dropwise to a stirred solution of α-azido amide (1.0 equiv), *p*-toluenesulfonyl (tosyl) hydrazide (5.0 equiv), and pyrrolidine (5.0 equiv) in DMSO (0.2 M based on an azido substrate unless otherwise noted) at 25 °C (set by a water bath) under the nitrogen gas atmosphere. After completion of the reaction checked by TLC, the mixture was diluted with ether and quenched with water. The solution was extracted three times with ether and was washed with water and brine. The collected organic layer was dried over sodium sulfate. Concentration and purification by flash neutral silica gel column chromatography gave the diazo product.

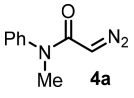
From Ketones. Pyrrolidine (2.5 equiv) was added dropwise to a stirred solution of α-azido ketone (1.0 equiv) and *p*-toluenesulfonyl hydrazide (5.0 equiv) in DMSO (0.2 M based on an azido substrate unless otherwise noted) at 25 °C (set by a water bath) under the nitrogen gas atmosphere. The purification procedure was followed for amides.



2a

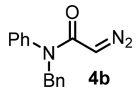
*N-(3-Azidopropyl)-2-diazo-N-phenylacetamide (**2a**).* The following is a 0.10 mmol scale reaction: 20.5 mg of **2a** (84%) was obtained from the reaction with diazide **1a** (25.8 mg, 0.10 mmol), tosyl hydrazide (93.8 mg, 0.50 mmol, 5.0 equiv), pyrrolidine (42.0 μL, 0.50 mmol, 5.0 equiv), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 equiv) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 8/1 to 5/1).

The following is a 1.0 mmol scale reaction: 219.5 mg of **2a** (90%) was obtained from the reaction with diazide **1a** (259.1 mg, 1.0 mmol), tosyl hydrazide (931.9 mg, 5.0 mmol, 5.0 equiv), pyrrolidine (0.42 mL, 5.0 mmol, 5.0 equiv), and TBAF (3.6 mL, 1.0 M in THF, 3.6 mmol, 3.6 equiv) in DMSO (5.0 mL, 0.2 M) for 1 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 5/1 to 4/1 to 3/1 to 2/1). Compound **2a**: pale yellow oil; R_f value 0.63 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2102, 1622, 1592, 1401, 1263 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, 2H, J = 8.0, 7.5 Hz), 7.37 (t, 1H, J = 8.0 Hz), 7.19 (d, 2H, J = 7.5 Hz), 4.42 (s, 1H), 3.84 (t, 2H, J = 7.0 Hz), 3.36 (t, 2H, J = 6.5 Hz), 1.83 (tt, 2H, J = 7.0, 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 141.3, 129.9, 128.3, 128.2, 49.1, 47.4, 46.7, 27.7; HRMS (CI) calcd for $C_{11}H_{13}N_6O$ $[M + H]^+$ 245.1151, found 245.1152.



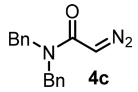
4a

*2-Diazo-N-methyl-N-phenylacetamide (**4a**).*[32] A total of 13.2 mg of **4a** (75%) was obtained from the reaction with azide **3a** (19.0 mg, 0.10 mmol), tosyl hydrazide (93.6 mg, 0.50 mmol, 5.0 equiv), pyrrolidine (42.0 μL, 0.50 mmol, 5.0 equiv), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 equiv) in DMSO (0.5 mL, 0.2 M) for 1.5 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 8/1): pale yellow oil; R_f value 0.57 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2106, 1622, 1591, 1387 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, 2H, J = 7.5 Hz), 7.33 (t, 1H, J = 7.5 Hz), 7.20 (m, 2H), 4.51 (s, 1H), 3.32 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 143.1, 129.8, 127.9, 127.3, 47.3, 37.1; HRMS (CI) calcd for $C_9H_{10}N_3O$ $[M + H]^+$ 176.0824, found 176.0826.



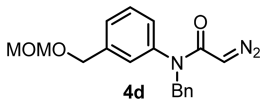
4b

*N-Benzyl-2-diazo-N-phenylacetamide (**4b**).*[32] A total of 21.8 mg of **4b** (87%) was obtained from the reaction with azide **3b** (26.6 mg, 0.10 mmol), tosyl hydrazide (93.5 mg, 0.50 mmol, 5.0 equiv), pyrrolidine (42.0 μL, 0.50 mmol, 5.0 equiv), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 equiv) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 8/1): pale yellow amorphous solid; R_f value 0.63 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 3478, 2106, 1624, 1593, 1399 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.22 (m, 8H), 7.03–7.01 (m, 2H), 4.93 (s, 2H), 4.45 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 141.4, 137.5, 129.6, 128.6, 128.43, 128.36, 128.1, 127.3, 52.9, 47.4; HRMS (CI) calcd for $C_{15}H_{14}N_3O$ $[M + H]^+$ 252.1137, found 252.1143.



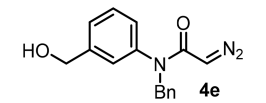
4c

*N,N-Dibenzyl-2-diazoacetamide (**4c**).* A total of 20.9 mg of **4c** (79%) was obtained from the reaction with azide **3b** (28.0 mg, 0.10 mmol), tosyl hydrazide (93.7 mg, 0.50 mmol, 5.0 equiv), pyrrolidine (42.0 μL, 0.50 mmol, 5.0 equiv), and TBAF (0.44 mL, 1.0 M in THF, 0.44 mmol, 4.4 equiv) in DMSO (0.5 mL, 0.2 M) for 3 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 6/1): pale yellow oil; R_f value 0.63 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2106, 1605, 1428, 1213 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.34 (m, 4H), 7.31–7.28 (m, 2H), 7.23 (br-s, 4H), 4.99 (s, 1H), 4.62–4.29 (br-m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 136.6 (br), 128.8, 127.6, 126.4 (br), 49.4 (br), 47.0; HRMS (CI) calcd for $C_{16}H_{16}N_3O$ $[M + H]^+$ 266.1293, found 266.1295.



4d

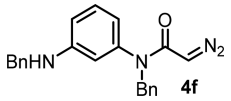
*N-Benzyl-2-diazo-N-(3-((methoxymethoxy)methyl)phenyl)-acetamide (**4d**).* A total of 28.1 mg of **4d** (87%) was obtained from the reaction with azide **3d** (34.0 mg, 0.10 mmol), tosyl hydrazide (93.6 mg, 0.50 mmol, 5.0 equiv), pyrrolidine (42.0 μL, 0.50 mmol, 5.0 equiv), and TBAF (0.36 mL, 0.36 mmol, 3.6 equiv) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 10/1 to 6/1 to 4/1): pale yellow oil; R_f value 0.6 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2932, 2885, 2107, 1625, 1603, 1587, 1399 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.21 (m, 7H), 7.04 (s, 1H), 6.93 (ddd, 1H, J = 6.0, 2.5, 1.5 Hz), 4.92 (s, 2H), 4.66 (s, 2H), 4.53 (s, 2H), 4.46 (s, 1H), 3.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 141.5, 139.9, 137.4, 129.6, 128.6, 128.3, 127.6, 127.4, 127.32, 127.30, 95.8, 68.3, 55.4, 52.8, 47.4; HRMS (MALDI-TOF) calcd for $C_{18}H_{19}N_3NaO_3$ $[M + Na]^+$ 348.1324, found 348.1314.



4e

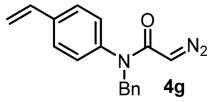
DOI: 10.1021/acs.joc.8b02074
J. Org. Chem. XXXX, XXX, XXX–XXX

*N-Benzyl-2-diazo-N-(3-(hydroxymethyl)phenyl)acetamide (**4e**).* A total of 13.0 mg of **4e** (46%) was obtained from the reaction with azide **3e** (29.5 mg, 0.10 mmol), tosyl hydrazide (93.2 mg, 0.50 mmol, 5.0 equiv), pyrrolidine (42.0 μL, 0.50 mmol, 5.0 equiv), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 equiv) in DMSO (0.5 mL, 0.2 M) for 3 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 1/1) and GPC for further purification: pale yellow oil; R_f value 0.5 (hexane/ethyl acetate = 1/2); IR (NaCl, neat) ν_{max} 3396, 3117, 2106, 1584, 1403 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.21 (m, 7H), 7.05 (s, 1H), 6.93 (ddd, 1H, J = 5.0, 1.5, 1.5 Hz), 4.92 (s, 2H), 4.66 (d, 2H, J = 5.5 Hz), 4.46 (s, 1H), 1.82−1.78 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 142.9, 141.5, 137.4, 129.6, 128.5, 128.4, 127.4, 126.5, 126.4, 64.3, 52.9, 47.5; HRMS (CI) calcd for $C_{16}H_{16}N_3O_2$ $[M + H]^+$ 282.1243, found 282.1236.



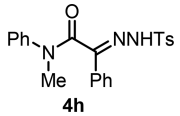
4f

*N-Benzyl-N-(3-(benzylamino)phenyl)-2-diazoacetamide (**4f**).* A total of 17.2 mg of **4f** (48%) was obtained from the reaction with azide **3f** (37.0 mg, 0.10 mmol), tosyl hydrazide (93.2 mg, 0.50 mmol, 5.0 equiv), pyrrolidine (42.0 μL, 0.50 mmol, 5.0 equiv), and TBAF (0.50 mL, 1.0 M in THF, 0.50 mmol, 5.0 equiv) in DMSO (0.5 mL, 0.2 M) for 6 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 10/1 to 8/1 to 6/1): pale yellow oil; R_f value 0.77 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2102, 1597, 1492, 1399, 1346 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, 2H, J = 7.0, 5.5 Hz), 7.33−7.21 (m, 8H), 7.08 (dd, 1H, J = 8.0, 8.0 Hz), 6.55 (dd, 1H, J = 8.5, 2.0 Hz), 6.35 (dd, 1H, J = 7.5, 1.0 Hz), 6.21 (dd, 1H, J = 2.0, 2.0 Hz), 4.86 (s, 2H), 4.52 (s, 1H), 4.23 (s, 2H), 4.19 (br, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 148.9, 142.5, 138.6, 137.8, 130.1, 128.7, 128.5, 128.3, 127.40, 127.36, 127.2, 116.8, 112.6, 112.2, 52.7, 47.9, 47.3; HRMS (MALDI-TOF) calcd for $C_{22}H_{20}N_4ONa$ $[M + Na]^+$ 379.1535, found 379.1529.



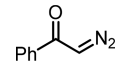
4g

*N-Benzyl-2-diazo-N-(4-vinylphenyl)acetamide (**4g**).* A total of 23.9 mg of **4g** (87%) was obtained from the reaction with azide **3g** (29.1 mg, 0.10 mmol), tosyl hydrazide (93.1 mg, 0.50 mmol, 5.0 equiv), pyrrolidine (42.0 μL, 0.50 mmol, 5.0 equiv), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 equiv) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 10/1 to 8/1): pale yellow oil; R_f value 0.8 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2106, 1624, 1600, 1509, 1396 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, 2H, J = 8.5 Hz), 7.29−7.22 (m, 5H), 6.97 (d, 2H, J = 8.0 Hz), 6.67 (dd, 1H, J = 17.0, 11.0 Hz), 5.74 (d, 1H, J = 17.0 Hz), 5.29 (d, 1H, J = 11.0 Hz), 4.92 (s, 2H), 4.49 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 140.7, 137.4, 137.3, 135.5, 128.6, 128.5, 128.4, 127.4, 127.2, 115.2, 52.8, 47.4; LRMS (EI, M = $C_{17}H_{15}N_3O$) m/z 277 (M^+, 2%), 249 (48), 158 (10), 130 (11), 91 (100); HRMS (EI) calcd for $C_{17}H_{15}N_3O$ (M^+) 277.1215, found 277.1208.



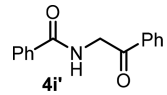
4h

*N-Methyl-N,2-diphenyl-2-(2-tosylhydrazineylidene)acetamide (**4h**, CCDC No. 1839202).* TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 equiv) was added dropwise to a stirred solution of azide **3h** (26.6 mg, 0.10 mmol) and tosyl hydrazide (93.5 mg, 0.50 mmol, 5.0 equiv) in DMSO (0.5 mL, 0.2 M) at 25 °C under a nitrogen atmosphere. The reaction mixture was diluted with diethyl ether and quenched with a saturated aqueous sodium bicarbonate solution after stirring for 1 h. The mixture was extracted three times with ether and was washed with water and brine. The collected organic layer was dried over sodium sulfate. Concentration and purification by neutral silica gel column chromatography (hexane/ethyl acetate = 5/1 to 2/1) followed by GPC for further purification gave tosyl hydrazone **4h** (30.1 mg, 0.0739 mmol, 74%). Recrystallization for X-ray analysis was performed with hexane/ether by the vapor diffusion method. Compound **4h**: colorless crystal; R_f value 0.27 (hexane/ethyl acetate = 1/1); mp 183−184 °C; IR (NaCl, neat) ν_{max} 1640, 1594, 1496, 1389, 1348, 1169, 1082, 915 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major isomer) δ 8.70 (d, 1H, J = 5.0 Hz), 7.84 (d, 2H, J = 8.0 Hz), 7.27−7.26 (m, 2H), 7.23−7.18 (m, 3H), 7.14−7.07 (m, 5H), 6.93−6.71 (m, 2H), 3.43 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 163.6, 150.9, 144.1, 140.4, 135.2, 132.5, 129.8, 129.6, 129.2, 128.3, 128.1, 128.0, 126.1, 125.8, 36.4, 21.6; HRMS (ESI) calcd for $C_{22}H_{21}N_3NaO_3S$ $[M + Na]^+$ 430.1201, found 430.1197.



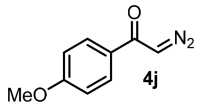
4i

*α-Diazo Acetophenone (**4i**)..*[19b,25a] A total of 10.7 mg of **4i** (74%) was obtained from the reaction with azide **3i** (16.0 mg, 0.10 mmol), tosyl hydrazide (93.5 mg, 0.50 mmol, 5.0 equiv), and pyrrolidine (21.0 μL, 0.25 mmol, 2.5 equiv) in DMSO (0.5 mL, 0.2 M) for 0.5 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 15/1): pale yellow solid; R_f value 0.37 (hexane/ethyl acetate = 3/1); mp 45 °C; IR (NaCl, neat) ν_{max} 2106, 1613, 1364, 1227 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77−7.76 (m, 2H), 7.55 (tt, 1H, J = 7.5, 1.5 Hz), 7.47−7.44 (m, 2H), 5.91 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.3, 136.6, 132.7, 128.6, 126.7, 54.2; HRMS (CI) calcd for $C_8H_7N_2O$ $[M + H]^+$ 147.0558, found 147.0547.



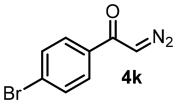
4i'

*N-(2-Oxo-2-phenylethyl)benzamide (**4i'**, CCDC No. 1839204), Dimeric Compound from **3i**.* To a stirred solution of azido ketone **3i** (16.2 mg, 0.10 mmol) in DMSO (1.0 mL, 0.1 M) was added TBAF (0.22 mL, 1.0 M in THF, 0.22 mmol, 2.2 equiv) at 25 °C. After 15 min, the reaction was quenched with water, and the mixture was extracted twice with ether. The combined organic layer was washed with brine and was dried over sodium sulfate. Concentration and purification by neutral silica gel column chromatography (hexane/ethyl acetate = 10/1 to 5/1) gave 5.0 mg of compound **4i'** (42%). Recrystallization for X-ray analysis was performed with hexane/ethyl acetate by the vapor diffusion method. Compound **4i'**: yellow crystal; R_f value 0.27 (hexane/ethyl acetate = 2/1); mp 115−116 °C; IR (NaCl, neat) ν_{max} 3330, 3061, 2924, 1698, 1645, 1537, 1488, 1225 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, 2H, J = 8.5, 1.0 Hz), 7.88 (dd, 2H, J = 8.0, 1.5 Hz), 7.05 (m, 1H), 7.55−7.51 (m, 3H), 7.47 (dd, 2H, J = 8.0, 6.5 Hz), 7.34 (br, 1H), 4.96 (d, 2H, J = 4.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.2, 167.4, 134.3, 134.2, 133.8, 131.8, 129.0, 128.6, 128.0, 127.1, 46.9; LRMS (EI, M = $C_{15}H_{13}NO_2$) m/z 239 (20%, M^+), 211 (18), 134 (20), 105 (100); HRMS (EI) calcd for $C_{15}H_{13}NO_2$ (M^+) 239.0946, found 239.0952.



4j

*2-Diazo-1-(4-methoxyphenyl)ethan-1-one (**4j**)..*[19b,25a] A total of 13.2 mg of **4j** (75%) was obtained from azide **3j** (19.1 mg, 0.10 mmol), tosyl hydrazide (93.9 mg, 0.50 mmol, 5.0 equiv), and pyrrolidine (21.0 μL, 0.25 mmol, 2.5 equiv) in DMSO (0.5 mL, 0.2 M) for 3 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 6/1): pale yellow solid; R_f value 0.50 (hexane/ethyl acetate = 1/1); mp 75−76 °C; IR (NaCl, neat) ν_{max} 3099, 2115, 1611, 1590, 1567, 1388, 1372 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, 2H, J = 9.0 Hz), 6.93 (d, 2H, J = 9.0 Hz), 5.85 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.2, 163.2, 129.4, 128.7, 113.8, 55.4, 53.5; LRMS (EI, M = $C_9H_8N_2O_2$) m/z 176 (79%, M^+), 135 (100), 120 (28), 91 (35), 77 (52); HRMS (EI) calcd for $C_9H_8N_2O_2$ (M^+) 176.0586, found 176.0589.



4k

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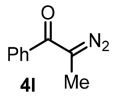
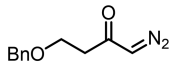
J. Org. Chem. XXXX, XXX, XXX−XXX

*1-(4-Bromophenyl)-2-diazoethan-1-one (**4k**)*..[19b,25a] A total of 13.0 mg of **4k** (58%) was obtained from the reaction with azide **3k** (17.4 mg, 0.10 mmol), tosyl hydrazide (93.1 mg, 0.50 mmol, 5.0 equiv), and pyrrolidine (21.0 μL, 0.25 mmol, 2.5 equiv) in DMSO (0.5 mL, 0.2 M) for 0.5 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1): pale yellow solid; R_f value 0.37 (hexane/ethyl acetate = 3/1); mp 110−111 °C; IR (KBr, disc) ν_{max} 3115, 2118, 1608, 1590, 1401, 1379, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, 2H, J = 8.5 Hz), 7.59 (d, 2H, J = 8.5 Hz), 5.88 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.1, 135.3, 131.9, 128.2, 127.6, 54.4; LRMS (EI, M = $C_8H_5BrN_2O$) m/z 226 (42%, M$^+$ of ^{81}Br), 224 (42, M$^+$ of ^{79}Br), 185 (55), 183 (56), 89 (100); HRMS (EI) calcd for $C_8H_5{}^{79}BrN_2O$ (M$^+$) 223.9585, found 223.9589.



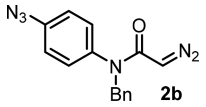
4l

*2-Diazo-1-phenylpropan-1-one (**4l**)*. A total of 10.0 mg of **4l** (63%) was obtained from the reaction with azide **3l** (17.4 mg, 0.10 mmol), tosyl azide (93.1 mg, 0.50 mmol, 5.0 equiv), and pyrrolidine (21.0 μL, 0.25 mmol, 2.5 equiv) in DMSO (1.0 mL, 0.1 M) for 0.5 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 20/1): pale yellow oil; R_f value 0.40 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{max} 2071, 1606, 1344, 1003 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59−7.57 (m, 2H), 7.50−7.47 (m, 1H), 7.44−7.41 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.2, 137.6, 131.3, 128.5, 127.1, 29.7, 9.5; LRMS (EI, M = $C_9H_8N_2O$) m/z 160 (16%, M$^+$), 132 (24), 104 (100), 103 (78), 77 (59), 51 (32); HRMS (EI) calcd for $C_9H_8N_2O$ (M$^+$) 160.0637, found 160.0631.



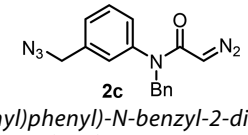
4m

*4-(Benzyloxy)-1-diazobutan-2-one (**4m**)*. A total of 10.3 mg of **4m** (51%) was obtained from the reaction with azide **3m** (21.8 mg, 0.10 mmol), tosyl hydrazide (93.5 mg, 0.50 mmol, 5.0 equiv), and pyrrolidine (21.0 μL, 0.25 mmol, 2.5 equiv) in DMSO (1.0 mL, 0.1 M) for 4 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1): pale yellow oil; R_f value 0.60 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2866, 2104, 1637, 1369, 1322, 1097 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 5.36 (s, 1H), 4.52 (s, 2H), 3.76 (t, 2H, J = 6.5 Hz), 2.59 (br-s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.0, 137.9, 128.4, 127.68, 127.66, 73.2, 65.8, 55.1, 41.3; HRMS (CI) calcd for $C_{11}H_{13}N_2O_2$ [M + H]$^+$ 205.0977, found 205.0979.



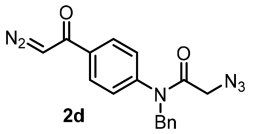
2b

*N-(4-Azidophenyl)-N-benzyl-2-diazoacetamide (**2b**)*. A total of 23.9 mg of **2b** (82%) was obtained from the reaction with diazide **1b** (30.6 mg, 0.10 mmol), tosyl hydrazide (93.6 mg, 0.50 mmol, 5.0 equiv), pyrrolidine (42.0 μL, 0.50 mmol, 5.0 equiv), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 equiv) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 15/1 to 10/1): pale yellow oil; R_f value 0.37 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{max} 2107, 1623, 1505, 1397, 1294, 1280 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.24 (m, 3H), 7.21−7.19 (m, 2H), 7.00−6.95 (m, 4H), 4.89 (s, 2H), 4.43 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 139.9, 137.8, 137.2, 129.9, 128.6, 128.4, 127.5, 120.0, 52.8, 47.4; LRMS (EI, M = $C_{15}H_{12}N_6O$) m/z 292 (3%, M$^+$), 264 (52), 236 (27), 223 (24), 196 (18), 91 (100), 84 (19); HRMS (EI) calcd for $C_{15}H_{12}N_6O$ (M$^+$) 292.1073, found 292.1071.



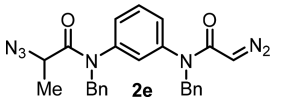
2c

*N-(3-(Azidomethyl)phenyl)-N-benzyl-2-diazoacetamide (**2c**)*. A total of 27.1 mg of **2c** (89%) was obtained from the reaction with diazide **1c** (32.1 mg, 0.10 mmol), tosyl hydrazide (93.8 mg, 0.50 mmol, 5.0 equiv), pyrrolidine (42.0 μL, 0.50 mmol, 5.0 equiv), and TBAF (0.36 mL, 0.36 mmol, 3.6 equiv) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 8/1): pale yellow oil; R_f value 0.23 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{max} 2104, 1623, 1397, 706 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, 1H, J = 8.0 Hz), 7.29−7.24 (m, 4H), 7.23−7.21 (m, 2H), 7.00−6.98 (m, 2H), 4.93 (s, 2H), 4.44 (s, 1H), 4.29 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 141.9, 137.3, 137.1, 130.1, 128.6, 128.5, 128.3, 128.1, 127.9, 127.5, 54.0, 52.9, 47.6; HRMS (CI) calcd for $C_{16}H_{15}N_6O$ [M + H]$^+$ 307.1307, found 307.1304.



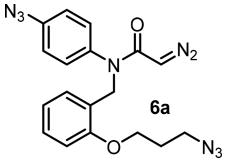
2d

*2-Azido-N-benzyl-N-(4-(2-diazoacetyl)phenyl)acetamide (**2d**, CCDC No.1839203)*. A total of 21.5 mg of **2d** (65%) as a pale yellow oil was obtained from the reaction with diazide **1d** (34.8 mg, 0.10 mmol), tosyl hydrazide (93.5 mg, 0.50 mmol, 5.0 equiv), and pyrrolidine (21.0 μL, 0.25 mmol, 2.5 equiv) in DMSO (0.5 mL, 0.2 M) for 0.5 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 2/1). Solid **2d** was obtained after storage in a refrigerator. Recrystallization for X-ray analysis was performed with hexane/ethyl acetate by the vapor diffusion method. Compound **2d**: pale yellow solid; R_f value 0.37 (hexane/ethyl acetate = 1/1); mp 65−66 °C; IR (NaCl, neat) ν_{max} 2105, 1671, 1602, 1361 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, 2H, J = 8.0 Hz), 7.28−7.26 (m, 3H), 7.17 (dd, 2H, J = 4.0, 3.5 Hz), 7.06 (d, 2H, J = 7.5 Hz), 5.87 (s, 1H), 4.91 (s, 2H), 3.60 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.7, 166.9, 144.0, 136.6, 136.0, 128.9, 128.6, 128.5, 128.3, 127.9, 54.8, 53.3, 50.9; LRMS (EI, M = $C_{17}H_{14}N_6O_2$) m/z 334 (18%, M$^+$), 250 (21), 222 (27), 187 (28), 174 (62), 118 (71), 91 (100); HRMS (EI) calcd for $C_{17}H_{14}N_6O_2$ (M$^+$) 334.1178, found 334.1177.



2e

*2-Azido-N-benzyl-N-(3-(N-benzyl-2-diazoacetamido)phenyl)-propanamide (**2e**)*. A total of 23.1 mg of **2e** (51%) was obtained from the reaction with diazide **1e** (46.9 mg, 0.10 mmol), tosyl hydrazide (93.5 mg, 0.50 mmol, 5.0 equiv), pyrrolidine (42.0 μL, 0.50 mmol, 5.0 equiv), and TBAF (0.36 mL, 0.36 mmol, 3.6 equiv) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 10/1 to 4/1) and GPC for further purification: pale yellow oil; R_f value 0.67 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2107, 1665, 1595, 1395, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, 1H, J = 7.5 Hz), 7.25−7.22 (m, 6H), 7.10−7.03 (m, 6H), 6.40 (s, 1H), 4.94−4.75 (m, 4H), 3.90 (s, 1H), 3.25 (q, 1H, J = 6.0 Hz), 1.29 (d, 3H, J = 6.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 165.3, 142.2, 141.2, 136.7, 136.1, 130.9, 129.4, 129.0, 128.6, 128.5, 128.0, 127.8, 127.7, 127.5, 54.1, 53.0, 52.4, 47.4, 16.3; HRMS (ESI) calcd for $C_{25}H_{23}N_7NaO_2$ [M + Na]$^+$ 476.1811, found 476.1804.



6a

*N-(4-Azidophenyl)-N-(2-(3-azidopropoxy)benzyl)-2-diazoacetamide (**6a**)*. A total of 30.6 mg of **6a** (78%) was obtained from triazide **5a** (40.6 mg, 0.10 mmol), tosyl hydrazide (93.7 mg, 0.50 mmol, 5.0 equiv), pyrrolidine (42.0 μL, 0.50 mmol, 5.0 equiv), and TBAF (0.36 mL, 0.36 mmol, 3.6 equiv) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 8/1 to 6/1): pale yellow oil; R_f value 0.77 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2103, 1623, 1505, 1396, 1287, 1244 cm^{-1}; ^{1}H NMR

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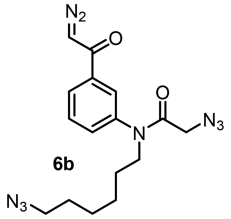
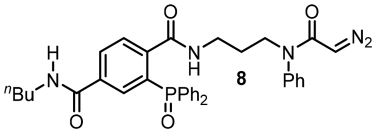
(500 MHz, $CDCl_3$) δ 7.26−7.25(m, 1H), 7.20 (ddd, 1H, J = 8.0, 8.0, 1.5 Hz), 7.02 (d, 2H, J = 8.5 Hz), 6.94 (d, 2H, J = 8.5 Hz), 6.89 (dd, 1H, J = 7.5, 7.5 Hz), 6.78 (d, 1H, J = 8.0 Hz), 4.96 (s, 2H), 4.44 (s, 1H), 3.91 (t, 2H, J = 6.0 Hz), 3.38 (t, 2H, J = 7.0 Hz), 1.89 (tt, 2H, J = 7.5, 6.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 156.3, 139.8, 138.2, 130.4, 129.8, 128.8, 125.2, 120.8, 119.8, 110.9, 64.2, 48.0, 47.4, 47.3, 28.7; LRMS (EI, M = $C_{18}H_{17}N_9O_2$) m/z 391 (9%, M^+), 363 (42), 335 (26), 162 (24), 134 (100), 105 (45); HRMS (EI) calcd for $C_{18}H_{17}N_9O_2$ (M^+) 391.1505, found 391.1503.

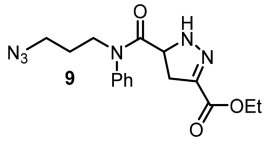


*2-Azido-N-(6-azidohexyl)-N-(3-(2-diazoacetyl)phenyl)acetamide (**6b**).* A total of 124.5 mg of **6b** (51%) was obtained from the reaction with triazide **5b** (253.1 mg, 0.658 mmol), tosyl hydrazide (613.0 mg, 3.29 mmol, 5.0 equiv), and pyrrolidine (137.5 μL, 1.65 mmol, 2.5 equiv) in DMSO (6.6 mL, 0.1 M) for 15 min followed by neutral silica gel column chromatography (hexane/ethyl acetate = 3/1 to 2/1): pale yellow oil; R_f value 0.4 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2105, 1670, 1578, 1362 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, 1H, J = 7.5 Hz), 7.63 (s, 1H), 7.55 (dd, 1H, J = 7.0, 7.0 Hz), 7.35 (d, 1H, J = 8.0 Hz), 5.92 (s, 1H), 3.73 (t, 2H, J = 7.5 Hz), 3.54 (s, 2H), 3.24 (t, 2H, J = 6.5 Hz), 1.60−1.50 (m, 4H), 1.40−1.31 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.5, 166.9, 141.3, 138.6, 132.0, 130.5, 126.7, 126.3, 55.0, 51.2, 50.9, 49.6, 28.7, 27.4, 26.3, 26.2; HRMS (ESI) calcd for $C_{16}H_{19}N_9NaO_2$ [M + Na]$^+$ 392.1559, found 392.1556.

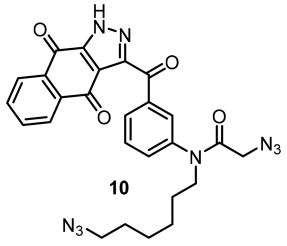
Conjugation Reactions Using Azido Diazo Substrates.



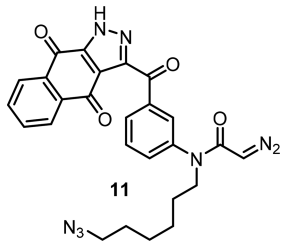
*N^4-Butyl-N^1-(3-(2-diazo-N-phenylacetamido)propyl)-2-(diphenylphosphoryl)terephthalamide (**8**).* To a stirred solution of alkyl azido α-diazo amido compound **2a** (11.2 mg, 0.05 mmol) in THF/water (1.0 mL, 0.05 M, 10/1) was added phosphine reagent **7** (31.8 mg, 0.075 mmol, 1.5 equiv), and the mixture was stirred at room temperature for 24 h. The resulting mixture was transferred to another flask with ethyl acetate and was concentrated in vacuo. The obtained crude material was purified by neutral silica gel column chromatography (hexane/ethyl acetate = 1/1 to dichloromethane/methanol = 15/1) followed by GPC, and 20.0 mg of the ligation product **8** (70%) was obtained: pale yellow amorphous solid; R_f value 0.17 (dichloromethane/methanol = 15/1); IR (NaCl, neat) ν_{max} 3286, 3061, 2931, 2106, 1645, 1542, 1407 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (t, 1H, J = 6.0 Hz), 7.99 (d, 1H, J = 8.5 Hz), 7.87 (dd, 1H, J = 13.5, 1.0 Hz), 7.83 (dd, 1H, J = 8.0, 4.0 Hz), 7.65−7.61 (m, 4H), 7.53−7.50 (m, 2H), 7.44−7.38 (m, 6H), 7.35−7.32 (m, 1H), 7.13 (d, 2H, J = 7.0 Hz), 6.53 (br-s, 1H), 4.37 (s, 1H), 3.69 (t, 2H, J = 7.0 Hz), 3.34 (dd, 2H, J = 12.0, 7.0 Hz), 2.94 (dd, 2H, J = 13.0, 7.0 Hz), 1.50 (ddt, 2H, J = 7.5, 7.5, 7.5 Hz), 1.42 (ddt, 2H, J = 7.0, 7.0, 7.0 Hz), 1.31 (qdd, 2H, J = 7.5, 7.5, 7.5 Hz), 0.90 (t, 3H, J = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8 (d, J = 3.1 Hz), 166.0, 165.6, 143.0 (d, J = 8.4 Hz), 141.1, 135.9 (d, J = 10.8 Hz), 132.4 (d, J = 10.8 Hz), 132.2 (d, J = 2.4 Hz), 131.9 (d, J = 10.8 Hz), 131.5, 130.8 (d, J = 2.4 Hz), 130.7, 130.4 (d, J = 8.4 Hz), 129.8, 128.55, 128.45, 128.32, 128.26, 47.3, 46.4, 39.8, 36.8, 31.4, 27.0, 20.0, 13.7; ^{31}P NMR (202 MHz, benzene-d_6) δ 32.9; HRMS (ESI) calcd for $C_{35}H_{36}N_5NaO_4P$ [M + Na]$^+$ 644.2403, found 644.2403.



*Ethyl 5-((3-Azidopropyl)(phenyl)carbamoyl)-4,5-dihydro-1H-pyrazole-3-carboxylate (**9**).* To a stirred solution of alkyl azido α-diazo amido compound **2a** (11.2 mg, 0.05 mmol) in acetonitrile/water (2.5 mL, 0.02 M, 1/1) was added ethyl acrylate (27.5 μL, 0.25 mmol, 5.0 equiv), and the mixture was stirred at room temperature for 24 h. After removal of solvent in vacuo, the resulting crude material was purified by neutral silica gel column chromatography (hexane/ethyl acetate = 3/1 to 2/1 to 1/1), and 13.5 mg of pyrazoline **9** (86%) was obtained: pale yellow oil; R_f value 0.37 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 3323, 2096, 1700, 1660, 1258, 1119 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, 2H, J = 8.0, 7.5 Hz), 7.42 (dd, 1H, J = 7.0, 6.5 Hz), 7.20 (d, 2H, J = 7.5 Hz), 6.43 (s, 1H), 4.41 (dd, 1H, J = 7.5, 7.0 Hz), 4.25 (q, 2H, J = 7.5 Hz), 3.85 (ddd, 1H, J = 14.5, 7.5, 7.0 Hz), 3.74 (ddd, 1H, J = 14.0, 7.5, 7.0 Hz), 3.34 (dd, 2H, J = 7.0, 6.5 Hz), 3.08 (dd, 1H, J = 17.0, 7.5 Hz), 2.77 (dd, 1H, J = 17.0, 7.5 Hz), 1.82 (tt, 1H, J = 7.5, 7.0 Hz), 1.31 (t, 3H, J = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 162.1, 142.6, 140.5, 130.4, 128.9, 128.5, 61.3, 60.5, 49.1, 47.8, 36.5, 27.0, 14.2; LRMS (EI, M = $C_{16}H_{20}N_6O_3$) m/z 344 (3%, M^+), 299 (19), 176 (25), 141 (87), 106 (48), 95 (100); HRMS (EI) calcd for $C_{16}H_{20}N_6O_3$ (M^+) 344.1597, found 344.1594.



*2-Azido-N-(6-azidohexyl)-N-(3-(4,9-dioxo-4,9-dihydro-1H-benzo[f]indazole-3-carbonyl)phenyl)acetamide (**10**).* To a stirred solution of diazido diazo compound **6b** (159.9 mg, 0.433 mmol) and 1,4-naphthoquinone (103.7 mg, 0.649 mmol, 1.5 equiv) in DMSO (8.7 mL, 0.05 M) was added cesium carbonate (282.6 mg, 0.866 mmol, 2.0 equiv) at room temperature under open-air conditions. After 2 h, the reaction was quenched with water, and the mixture was extracted three times with dichloromethane. The combined organic layer was washed three times with water and brine. The collected organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 2/1 to 1/1 to 1/1 + 5% methanol) gave 185.4 mg of pyrazole **10** (82%): pale blown amorphous solid; R_f value 0.2 (dichloromethane/methanol = 20/1); IR (NaCl, neat) ν_{max} 2934, 2105, 1681, 1582, 1331, 1255, 917 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27−8.24 (m, 2H), 8.17 (d, 1H, J = 8.0 Hz), 7.88 (s, 1H), 7.85−7.79 (m, 2H), 7.65 (dd, 1H, J = 8.0, 7.5 Hz), 7.47 (d, 1H, J = 8.5 Hz), 3.76 (t, 2H, J = 7.5 Hz), 3.64 (s, 2H), 3.30 (t, 2H, J = 7.0 Hz), 1.58−1.53 (m, 4H), 1.38−1.34 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.6, 177.8, 176.0, 167.4, 140.5, 138.0, 135.2, 134.5, 133.9, 133.0, 132.4, 130.55, 130.50, 130.3, 127.9, 127.0, 121.2, 51.4, 51.2, 49.6, 28.7, 27.3, 26.4, 26.2; HRMS (ESI) calcd for $C_{26}H_{23}N_9NaO_4$ [M + Na]$^+$ 548.1771, found 548.1778.



*N-(6-Azidohexyl)-2-diazo-N-(3-(4,9-dioxo-4,9-dihydro-1H-benzo[f]indazole-3-carbonyl)phenyl)acetamide (**11**).* To a solution of diazide **10** (133.9 mg, 0.255 mmol), tosyl hydrazide (237.8 mg, 1.27 mmol, 5.0 equiv), and pyrrolidine (106 μL, 1.27 mmol, 5.0 equiv) in DMSO (2.55 mL, 0.1 M) was added dropwise TBAF (1.53 mL, 1.0 M in THF, 1.53 mmol, 6.0 equiv) at 25 °C. After 4 h, the reaction mixture was diluted with dichloromethane and water. The mixture was extracted three times with dichloromethane, and the organic layer was washed twice with water. The collected organic layer was dried over

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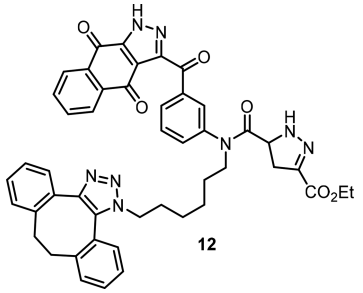
sodium sulfate. Concentration and purification by neutral silica gel column chromatography (dichloromethane to dichloromethane/methanol = 20/1) followed by GPC gave 97.2 mg of **11** (75%): pale blown amorphous solid; R_f value 0.47 (dichloromethane/methanol = 20/1); IR (NaCl, neat) ν_{max} 2934, 2860, 2106, 1682, 1578, 1407 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.27−8.25 (m, 1H), 8.22−8.21 (m, 1H), 8.12 (d, 1H, J = 8.0 Hz), 7.86 (s, 1H), 7.84−7.78 (m, 2H), 7.61 (dd, 1H, J = 8.0, 7.5 Hz), 7.49 (d, 1H, J = 8.0 Hz), 4.50−4.48 (m, 1H), 3.78 (t, 2H, J = 7.0 Hz), 3.29−3.26 (m, 2H), 1.57−1.51 (m, 4H), 1.39−1.30 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.9, 178.0, 176.0, 166.0, 141.5, 137.8, 135.0, 134.4, 133.9, 133.4, 132.5, 130.8, 130.2, 129.6, 127.7, 127.1, 121.1, 51.4, 49.1, 48.0, 28.7, 27.9, 26.4, 26.2; HRMS (ESI) calcd for $C_{26}H_{22}N_8NaO_4$ $[M + Na]^+$ 533.1662, found 533.1653.

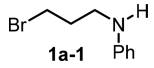


12

*Ethyl 5-((6-(8,9-Dihydro-1H-dibenzo[3,4:7,8]cycloocta[1,2-d]-[1,2,3]triazol-1-yl)hexyl)(3-(4,9-dioxo-4,9-dihydro-1H-benzo[f]-indazole-3-carbonyl)phenyl)carbamoyl)-4,5-dihydro-1H-pyrazole-3-carboxylate (**12**).* To a stirred solution of diazo azide **11** (55.6 mg, 0.109 mmol) in acetonitrile/water (5.5 mL, 1/1, 0.02 M) was added ethyl acrylate (59.5 μL, 0.545 mmol, 5.0 equiv) at room temperature. After 26 h, the wet organic solvent was removed under reduced pressure. Then, the resulting crude material was dissolved in acetonitrile (2.2 mL, 0.05 M). To a stirred acetonitrile solution was added dibenzocyclooctyne (5,6-dihydro-11,12-didehydrodibenzo[a,e]-cyclooctyne, 33.3 mg, 0.163 mmol, 1.5 equiv based on **11**)[33] at room temperature. After 24 h, the organic solvent was removed under reduced pressure to obtain crude material, which was purified by neutral silica gel column chromatography (hexane/ethyl acetate = 1/1 to dichloromethane to dichloromethane/methanol = 20/1) followed by GPC to afford 58.9 mg of **12** (66%): pale yellow amorphous solid; R_f value 0.23 (dichloromethane/methanol = 20/1); IR (NaCl, neat) ν_{max} 3330, 3065, 2933, 2860, 1682, 1581, 1454, 1434, 1334, 1221 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, 1H, J = 7.5 Hz), 8.19−8.15 (m, 2H), 7.91 (s, 1H), 7.78 (dd, 1H, J = 7.5 Hz), 7.73 (dd, 1H, J = 7.5 Hz), 7.65 (dd, 1H, J = 8.0 Hz), 7.62−7.57 (m, 1H), 7.33−7.30 (m, 2H), 7.23−7.12 (m, 6H), 4.43−4.41 (m, 2H), 4.27−4.24 (m, 1H), 4.19 (q, 2H, J = 7.5 Hz), 3.38−3.35 (m, 1H), 3.26−3.17 (m, 1H), 3.08 (dd, 2H, J = 11.0 Hz), 2.95−2.86 (m, 2H), 1.86 (br-s, 1H), 1.70 (m, 1H), 1.54−1.45 (m, 2H), 1.31−1.18 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.7, 177.9, 175.9, 170.4, 162.1, 146.4, 142.3, 141.5, 140.44, 140.40, 138.6, 137.57, 137.55, 134.8, 134.6, 134.07, and 134.04 (conformers), 133.6, 133.02, 132.99, 132.41, 131.84, 131.80, 130.8, 130.6, 130.2, 129.8, 129.36, 129.31, 128.8, 128.1, 127.8, 126.8, 126.5, 126.1, 121.5, 61.3, 60.8, and 60.7 (conformers), 50.1, 50.0, 48.1, 36.5, 32.8, 29.3, and 29.2 (conformers), 26.99 and 26.96 (conformers), 25.7, 25.61, and 25.55 (conformers), 14.13; HRMS (ESI) calcd for $C_{47}H_{42}N_8NaO_6$ $[M + Na]^+$ 837.3125, found 837.3107.

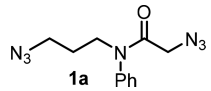
Preparation of Substrates. *General Procedure of the Synthesis of Azido Acetamides from Amines.* The following is reaction 1: in a two-neck flask, amine was dissolved in dichloromethane under a nitrogen atmosphere and the solution was cooled to 0 °C. Then, a solution of bromoacetyl bromide or 2-bromopropionyl bromide in dichloromethane was added slowly to the reaction mixture, in which precipitate was formed immediately. The reaction mixture was warmed to room temperature and was stirred for 1 h. The reaction was quenched with a saturated aqueous sodium bicarbonate solution, and the mixture was washed with saturated aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate. Concentration in vacuo gave the crude bromoacetamide product, which was used in the next step without further purification. (Beware of residual dichloromethane; see also the caution statement above.)

The following is reaction 2: to a stirred solution of crude bromoacetamide in DMSO was added sodium azide at ambient temperature. After completion of the reaction (reaction time noted in each compound section), the reaction was quenched with water, and the mixture was extracted three times with ether. The organic layer was washed with water and brine, and the combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography gave α-azido acetamide.



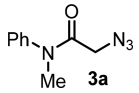
1a-1

*N-(3-Bromopropyl)aniline (**1a-1**).* A stirred solution of aniline (0.455 mL, 5.0 mmol) and 1,3-dibromopropane (3.05 mL, 30.0 mmol, 6.0 equiv) in acetonitrile (10 mL, 0.5 M) was heated up to reflux for 3 h. After the mixture cooled to room temperature, the reaction mixture was diluted with water and was extracted three times with ether. The combined organic layer was dried over magnesium sulfate. Concentration and purification by silica gel column chromatography (hexane with 5% ether to hexane/ethyl acetate = 5/1) gave **1a-1** (386 mg, 1.80 mmol, 36%): colorless oil; R_f value 0.5 (hexane/ethyl acetate = 5/1); IR (NaCl, neat) ν_{max} 3404, 1603, 1506, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (m, 2H), 6.73 (tt, 1H, J = 7.5, 1.0 Hz), 6.65 (m, 2H), 3.52 (t, 2H, J = 6.5 Hz), 3.35 (t, 2H, J = 6.0 Hz), 2.16 (tt, 2H, J = 6.5, 6.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6, 129.3, 117.7, 112.9, 42.0, 31.9, 31.2; LRMS (EI, M = $C_9H_{12}BrN$) m/z 215 (1.2%, M^+ of ^{81}Br), 213 (1.4, M^+ of ^{79}Br), 106 (100), 77 (15); HRMS (EI) calcd for $C_9H_{12}{}^{81}BrN$ (M^+) 215.0133, found 215.0123.



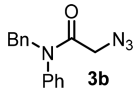
1a

*2-Azido-N-(3-azidopropyl)-N-phenylacetamide (**1a**).* According to the general procedure, 390 mg of **1a** (91% from amine for 2 steps) was obtained from the reactions with (1) **1a-1** (352 mg, 1.65 mmol, 1.0 equiv), bromoacetyl bromide (0.165 mL, 1.88 mmol, 1.14 equiv), which dissolved in dichloromethane (6 mL), and dichloromethane solvent (14 mL, 0.12 M); (2) crude bromoacetamide (574 mg), sodium azide (375 mg, 5.76 mmol, 3.5 equiv), and DMSO (8.3 mL, 0.2 M) for 1 h followed by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 2/1): pale yellow oil; R_f value 0.5 (hexane/ethyl acetate = 2/1); IR (NaCl, neat) ν_{max} 2935, 2104, 1670, 1493, 1406, 1261 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48−7.40 (m, 3H), 7.18−7.16 (m, 2H), 3.81 (t, 2H, J = 7.5 Hz), 3.57 (s, 2H), 3.37 (t, 2H, J = 7.0 Hz), 1.85 (tt, 2H, J = 7.5, 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 140.4, 130.3, 128.9, 127.8, 50.8, 49.0, 47.3, 27.1; HRMS (CI) calcd for $C_{11}H_{14}N_7O$ $[M + H]^+$ 260.1260, found 260.1264.



3a

*2-Azido-N-methyl-N-phenylacetamide (**3a**).* Following the general procedure, 916 mg of **3a** (97% from amine for 2 steps) was obtained from the reactions with (1) *N*-methyl aniline (0.54 mL, 5.0 mmol, 1.0 equiv), bromoacetyl bromide (0.50 mL, 5.7 mmol, 1.14 equiv) dissolved in dichloromethane (20 mL), and dichloromethane solvent (40 mL, 0.13 M); (2) crude bromoacetamide (1.230 g), sodium azide (810.3 mg, 12.5 mmol, 2.5 equiv), and DMSO (25 mL, 0.2 M) for 20 min followed by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 2/1): pale yellow oil; R_f value 0.67 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2924, 2106, 1668, 1595, 1495, 1390, 1267, 1124 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, 2H, J = 7.5, 7.5 Hz), 7.38 (t, 1H, J = 7.5 Hz), 7.19 (d, 2H, J = 7.5 Hz), 3.61 (s, 2H), 3.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 142.1, 130.2, 128.6, 127.0, 50.6, 37.5; LRMS (EI, M = $C_9H_{10}N_4O$) m/z 190 (1.1%, M^+), 162 (29), 134 (100), 105 (83), 77 (64); HRMS (EI) calcd for $C_9H_{10}N_4O$ (M^+) 190.0855, found 190.0858.



3b

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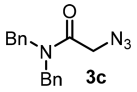
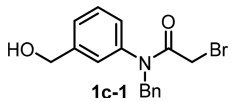
*2-Azido-N-benzyl-N-phenylacetamide (**3b**).* Following the general procedure, 1.30 g of **3b** (98% from amine for 2 steps) was obtained from the reactions with (1) *N*-benzylaniline (916 mg, 5.0 mmol, 1.0 equiv), bromoacetyl bromide (0.50 mL, 5.7 mmol, 1.14 equiv) dissolved in dichloromethane (20 mL), and dichloromethane solvent (40 mL, 0.13 M); (2) crude bromoacetamide (1.5380 g), sodium azide (817.5 mg, 12.6 mmol, 2.5 equiv), and DMSO (25 mL, 0.2 M) for 20 min followed by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 3/1): pale yellow oil; R_f value 0.2 (hexane/ethyl acetate = 5/1); IR (NaCl, neat) ν_{max} 2104, 1670, 1496, 1399, 1260 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.33 (m, 3H), 7.29−7.26 (m, 3H), 7.20−7.18 (m, 2H), 6.97−6.95 (m, 2H), 4.90 (s, 2H), 3.59 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2 140.2, 136.5, 129.9, 129.0, 128.8, 128.5, 128.2, 127.7, 53.4, 50.8; LRMS (EI, M = $C_{15}H_{14}N_4O$) *m*/*z* 266 (8%, M^+), 182 (53), 119 (58), 91 (100), 77 (45); HRMS (EI) calcd for $C_{15}H_{14}N_4O$ (M^+) 266.1168, found 266.1162.



3c

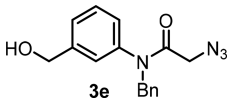
*2-Azido-N,N-dibenzylacetamide (**3c**).* Following the general procedure, 1.38 g of **3c** (99% from amine for 2 steps) was obtained from the reactions with (1) *N*,*N*-dibenzyl amine (0.96 mL, 5.0 mmol, 1.0 equiv), bromoacetyl bromide (0.495 mL, 5.7 mmol, 1.14 equiv) dissolved in dichloromethane (20 mL), and dichloromethane solvent (40 mL, 0.13 M); (2) crude bromoacetamide (1.666 g), sodium azide (812 mg, 12.5 mmol, 2.5 equiv), and DMSO (25 mL, 0.2 M) for 20 min followed by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 2/1): colorless oil; R_f value 0.8 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2104, 1658, 1450, 1213 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.29 (m, 6H), 7.26−7.24 (m, 2H), 7.34 (d, 2H, *J* = 7.0 Hz), 4.65 (s, 2H), 4.37 (s, 2H), 3.98 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 136.4, 135.4, 129.2, 128.7, 128.5, 128.0, 127.8, 126.2, 50.6, 49.3, 48.9; LRMS (EI, M = $C_{16}H_{16}N_4O$) *m*/*z* 280 (1.8%, M^+), 196 (51), 91 (100); HRMS (EI) calcd for $C_{16}H_{16}N_4O$ (M^+) 280.1324, found 280.1306.



1c-1

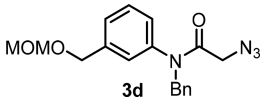
*N-Benzyl-2-bromo-N-(3-(hydroxymethyl)phenyl)acetamide (**1c-1**).* To a stirred solution of 3-aminobenzyl alcohol (616 mg, 5.0 mmol) in ethanol (8.3 mL, 0.6 M) was added benzaldehyde (0.61 mL, 5.0 mmol, 1.2 equiv) at room temperature. After 2 h, the mixture was cooled to 0 °C, and then sodium borohydride (632 mg, 15.0 mmol, 3.0 equiv) was added carefully. After the mixture stirred at room temperature for 12 h, the resulting mixture was poured into a saturated aqueous sodium bicarbonate solution. The organic components were extracted three times with ethyl acetate and were washed with brine. The combined organic layer was dried over sodium sulfate. Concentration in vacuo gave (3-(benzylamino)phenyl)methanol (1.14 g) as a crude material, which was submitted to the next step without purification.

To a solution of the crude amine (1.14 g) in dichloromethane (40 mL, 0.13 M) was added bromoacetyl bromide (0.49 mL, 5.7 mmol, 1.14 equiv) dissolved in dichloromethane (20 mL) at 0 °C. After the mixture stirred at room temperature for 1 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution at 0 °C. The resulting mixture was washed with a saturated aqueous sodium bicarbonate solution and was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 8/1 to 5/1 to 3/1 to 2/1 to 1/1) gave 522 mg of **1c-1** (31% from amine for 2 steps): colorless oil; R_f value 0.40 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 3410, 1656, 1439, 1401, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.31 (m, 2H), 7.29−7.24 (m, 3H), 7.19−7.18 (m, 2H), 7.10 (s, 1H), 6.95 (d, 1H, *J* = 7.0 Hz), 4.88 (s, 2H), 4.67 (s, 2H), 3.67 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 143.0, 141.3, 136.5, 129.8, 128.8, 128.5, 127.6, 127.2, 126.9, 126.2, 64.2, 53.6, 27.4; LRMS (EI, M = $C_{16}H_{16}BrNO_2$) *m*/*z* 335 (0.8%, M^+ of ^{81}Br), 333 (0.8, M^+ of ^{79}Br), 254 (61), 236 (51), 132 (40), 91 (100); HRMS (EI) calcd for $C_{16}H_{16}{}^{79}BrNO_2$ (M^+) 333.0364, found 333.0368.



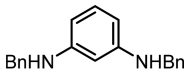
3e

*2-Azido-N-benzyl-N-(3-(hydroxymethyl)phenyl)acetamide (**3e**).* To a stirred solution of bromide **1c-1** (790.6 mg, 2.4 mmol) in DMSO (12 mL, 0.2 M) at ambient temperature was added sodium azide (308 mg, 4.73 mmol, 2.0 equiv). After 0.5 h, the resulting mixture was poured into water, and the mixture was extracted three times with ether. The organic layer was washed with water and brine. The combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (33% to 50% ethyl acetate in hexane) gave 700 mg of **3e** (99%): colorless oil; R_f value 0.17 (hexane/ethyl acetate = 2/1); IR (NaCl, neat) ν_{max} 2926, 2870, 2104, 1662, 1404, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.32 (m, 2H), 7.30−7.26 (m, 3H), 7.18 (d, 1H, *J* = 7.5 Hz), 7.18 (d, 1H, *J* = 6.5 Hz), 7.01 (s, 1H), 6.85−6.83 (m, 1H), 4.89 (s, 2H), 4.67 (d, 2H, *J* = 6.0 Hz), 3.60 (s, 2H), 1.94 (br, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 143.2, 140.4, 136.5, 130.0, 129.0, 128.5, 127.7, 127.2, 127.0, 126.2, 64.2, 53.4, 50.8; LRMS (EI, M = $C_{16}H_{16}N_4O_2$) *m*/*z* 296 (M^+, 1%), 268 (3), 238 (6), 136 (10), 118 (12), 91 (100); HRMS (EI) calcd for $C_{16}H_{16}N_4O_2$ (M^+) 296.1273, found 296.1271.



3d

*2-Azido-N-benzyl-N-(3-((methoxymethoxy)methyl)phenyl)-acetamide (**3d**).* To a stirred solution of alcohol **3e** (479 mg, 1.61 mmol) and tetrabutyl ammonium iodide (119 mg, 0.323 mmol, 0.2 equiv) in dichloromethane (16 mL, 0.1 M) were added *N*,*N*-diisopropylethylamine (1.13 mL, 6.46 mmol, 4.0 equiv) and chloromethyl methyl ether (0.365 mL, 4.84 mmol, 3.0 equiv) at 0 °C. After the mixture stirred at room temperature for 3 h, the resulting mixture was quenched by a saturated aqueous ammonium chloride solution. The organic components were extracted twice with dichloromethane and were washed with water and brine. The combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (25% to 33% to 50% ethyl acetate in hexane) gave 449 mg of **3d** (82%): colorless oil; R_f value 0.43 (hexane/ethyl acetate = 2/1); IR (NaCl, neat) ν_{max} 2932, 2886, 2105, 1671, 1046 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, 2H, *J* = 5.0 Hz), 7.29−7.23 (m, 3H), 7.20−7.18 (m, 2H), 6.98 (s, 1H), 6.58 (m, 1H), 4.89 (s, 2H), 4.66 (s, 2H), 4.53 (s, 2H), 3.60 (s, 2H), 3.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 140.3, 136.5, 129.8, 129.0, 128.4, 127.8, 127.6, 127.3, 127.1, 95.8, 68.1, 55.4, 53.3, 50.8; LRMS (EI, M = $C_{18}H_{20}N_4O_3$) *m*/*z* 340 (M^+, 0.2%), 312 (2), 250 (15), 91 (100); HRMS (EI) calcd for $C_{18}H_{20}N_4O_3$ (M^+) 340.1535, found 340.1528.



1e-1

*2-Azido-N-benzyl-N-phenylacetamide (**1e-1**).*[34] To a stirred solution of 1,3-phenylenediamine (1.08 g, 10 mmol) in ethanol (16.7 mL, 0.6 M) was added benzaldehyde (3.1 mL, 30 mmol, 3.0 equiv), and the mixture was stirred at room temperature for 0.5 h with a covered flask to protect from light. Then, the mixture was cooled to 0 °C, and sodium borohydride (1.69 g, 40 mmol, 4.0 equiv) was added carefully. After the mixture stirred at room temperature for 12 h, the resulting mixture was poured into a saturated aqueous sodium bicarbonate solution. The organic components were extracted three times with ethyl acetate and were washed with brine. The combined organic layer was dried over magnesium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 6/1) gave 2.75 g of *N*,*N*′-dibenzylamine **1e-1** (95%). This compound was soon submitted to the next step without collecting analytical data.

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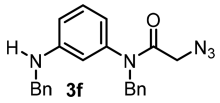
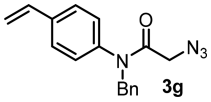


*2-Azido-N-benzyl-N-(3-(benzylamino)phenyl)acetamide (**3f**).* To a stirred solution of diamine **1e-1** (787 mg, 2.73 mmol) in dichloromethane (23 mL) was added bromoacetyl bromide (0.28 mL, 2.87 mmol, 1.05 equiv) dissolved in dichloromethane (10 mL) at 0 °C. After the mixture stirred at room temperature for 1 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution and was dried over sodium sulfate. Concentration in vacuo gave bromoacetamide (1.09 g) as a crude material, which was submitted to the next step without purification.

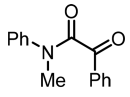
To a stirred solution of the bromide (1.09 g) in DMSO (14 mL, 0.2 M) was added sodium azide (354 mg, 5.46 mmol, 2.0 equiv) at room temperature. After 1 h, the reaction was quenched with water, and the organic components were extracted three times with ether. The organic layer was washed with water and brine. The combined organic layer was then dried over sodium sulfate. Concentration and purification by silica gel column chromatography (14% to 20% to 25% to 33% ethyl acetate in hexane) gave 429 mg of **3f** (42%): white solid; R_f value 0.43 (hexane/ethyl acetate = 2/1); mp 73.6−74.3 °C; IR (NaCl, neat) ν_{max} 3373, 3033, 2103, 1661, 1602, 1494 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.34 (m, 2H), 7.31−7.28 (m, 3H), 7.27−7.24 (m, 3H), 7.19 (dd, 2H, J = 7.5, 6.5 Hz), 7.09 (dd, 2H, J = 8.0, 8.0 Hz), 6.58 (dd, 1H, J = 8.0, 2.0 Hz), 6.26 (dd, 1H, J = 7.5, 1.0 Hz), 6.10 (dd, 1H, J = 2.5, 1.5 Hz), 4.82 (s, 2H), 4.22 (s, 3H), 3.57 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 149.1, 141.3, 138.4, 136.9, 130.4, 129.0, 128.7, 128.4, 127.53, 127.50, 127.3, 116.5, 113.3, 111.7, 53.2, 50.7, 47.9; LRMS (EI, M = $C_{22}H_{21}N_5O$) m/z 371 (M^+, 2%), 343 (88), 252 (37), 91 (100); HRMS (EI) calcd for $C_{22}H_{21}N_5O$ (M^+) 371.1746, found 371.1751.



*2-Azido-N-benzyl-N-(4-vinylphenyl)acetamide (**3g**).* To a stirred solution of 4-vinyl aniline (0.58 mL, 4.95 mmol) in ethanol (8.3 mL, 0.6 M) was added benzaldehyde (0.76 mL, 7.50 mmol, 1.5 equiv), and the mixture was stirred at room temperature for 1 h. Then, the mixture was cooled down to 0 °C, and sodium borohydride (631 mg, 15.0 mmol, 3.0 equiv) was added carefully. After the mixture stirred at room temperature for 12 h, the resulting mixture was poured into a saturated aqueous sodium bicarbonate solution. The organic components were extracted twice with ethyl acetate and were washed with brine. The combined organic layer was dried over magnesium sulfate. Concentration in vacuo gave benzylamine (1.27 g) as a crude material, which was submitted to the next step without purification.

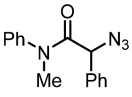
To a stirred solution of *N*-benzyl-4-vinylaniline (1.27 g) in dichloromethane (40 mL) was added bromoacetyl bromide (0.49 mL, 5.64 mmol, 1.14 equiv) dissolved in dichloromethane (20 mL) at 0 °C. After the mixture stirred at room temperature for 1 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution and was dried over sodium sulfate. Concentration in vacuo gave bromoacetamide (1.66 g) as a crude material, which was submitted to the next step without purification.

To a stirred solution of the bromide (1.66 g) in DMSO (25 mL, 0.2 M) was added sodium azide (646 mg, 9.90 mmol, 2.0 equiv) at room temperature. After 1 h, the reaction was quenched with water, and the organic components were extracted three times with ether. The organic layer was washed with water and brine. The combined organic layer was then dried over sodium sulfate. Concentration and purification by silica gel column chromatography (11% to 14% to 25% ethyl acetate in hexane) gave 551 mg of **3g** (38% for 3 steps): pale yellow oil; R_f value 0.47 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{max} 2103, 1669, 1508, 1397 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, 2H, J = 8.5 Hz), 7.29−7.26 (m, 3H), 7.19 (d, 1H, J = 7.5 Hz), 7.19 (d, 1H, J = 6.0 Hz), 6.91 (d, 2H, J = 8.5 Hz), 6.67 (dd, 1H, J = 18.0, 11.0 Hz), 5.75 (d, 1H, J = 18.0 Hz), 5.32 (d, 1H, J = 11.0 Hz), 4.89 (s, 2H), 3.61 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 139.5, 138.0, 136.5, 135.4, 129.0, 128.5, 128.3, 127.7, 127.6, 115.6, 53.3, 50.8; LRMS (EI, M = $C_{17}H_{16}N_4O$) m/z 292 (M^+, 4%), 208 (10), 145 (11), 118 (12), 91 (100); HRMS (EI) calcd for $C_{17}H_{16}N_4O$ (M^+) 292.1324, found 292.1324.



3h-1

*N-Methyl-2-oxo-N,2-diphenylacetamide (**3h-1**).*[35] To a stirred solution of benzoylformic acid (750 mg, 5.0 mmol) in dichloromethane (5 mL, 1 M) were added a catalytic amount of DMF (1 drop) and oxalyl chloride (0.475 mL, 5.5 mmol, 1.1 equiv) at room temperature. The reaction mixture was stirred at room temperature until generation of gas was stopped (1.5 h). Then, the reaction mixture was cooled to 0 °C. To the cooled mixture were added *N*-methyl aniline (0.81 mL, 7.5 mmol, 1.5 equiv) and triethylamine (1.75 mL, 12.5 mmol, 2.5 equiv). Then, the mixture was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted three times with ethyl acetate. The combined organic layer was washed with brine and was dried over magnesium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 1/1) gave 1.195 g of **3h-1** (100%): white solid; R_f value 0.63 (hexane/ethyl acetate = 1/1); mp 61−62 °C; IR (NaCl, neat) ν_{max} 1680, 1651, 1595, 1495, 1234 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major rotamer listed as similar to the referred referred) δ 7.85 (m, 2H), 7.57 (m, 1H), 7.46−7.42 (m, 2H), 7.25−7.20 (m, 3H), 7.14−7.13 (m, 2H), 3.49 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, major rotamer listed as the referred report) δ 190.8, 167.0, 141.1, 134.2, 133.4, 129.5, 129.4, 128.7, 128.1, 126.7, 36.2; LRMS (EI, M = $C_{15}H_{13}NO_2$) m/z 239 (26%, M^+), 134 (51), 105 (100), 77 (46); HRMS (EI) calcd for $C_{15}H_{13}NO_2$ (M^+) 239.0946, found 239.0968.



3h

*2-Azido-N-methyl-N,2-diphenylacetamide (**3h**).*[35] To an ice-cooled stirred solution of **3h-1** (1.13 g, 4.70 mmol) in ethanol and dichloromethane (11.5 mL, 2/1, 0.4 M) was added sodium borohydride (242 mg, 6.39 mmol, 1.36 equiv), and the reaction mixture was stirred at room temperature. After 1 h, the reaction was quenched by the careful addition of a saturated aqueous ammonium chloride solution, and the mixture was extracted three times with ethyl acetate. The combined organic extract was washed with brine and was dried over magnesium sulfate. Removal of organic solvents gave the crude material, which was used for the next step without further purification.

To an ice-cooled stirred solution of the crude alcohol in dichloromethane (4.7 mL, 1 M) were added triethylamine (1.94 mL, 13.8 mmol, 2.94 equiv) and methanesulfonyl chloride (0.462 mL, 5.97 mmol, 1.27 equiv, with slow addition), and the reaction mixture was stirred at the same temperature. After 1 h, the reaction was quenched with water, and organic materials were extracted three times with ethyl acetate. The combined organic layer was washed with brine and was dried over magnesium sulfate. Removal of organic solvents afforded the crude mesylate compound, which was submitted to the next step without further purification. (Beware of residual dichloromethane; see also the caution statement above.)

To an ice-cooled stirred solution of the crude mesylate material in DMF (4.7 mL, 1 M) was added sodium azide (657 mg, 7.03 mmol, 1.5 equiv), and the mixture was stirred at room temperature. After 3 h, the reaction was quenched with water, and the organic components were extracted three times with ether. The combined extracts were washed with water and brine. The combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 5/1) gave 1.01 g of **3h** (80% for 3 steps): white solid; R_f value 0.60 (hexane/ethyl acetate = 2/1); mp 81−82 °C; IR (NaCl, neat) ν_{max} 2098, 1666, 1491, 1387, 1236 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.29 (m, 6H), 7.13−7.11

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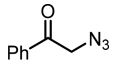
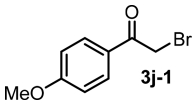
(m, 2H), 6.90 (br-s, 2H), 4.61 (s, 1H), 3.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 142.1, 134.2, 129.7, 129.0, 128.9, 128.5, 128.0, 127.6, 62.8, 37.8; HRMS (CI) calcd for $C_{15}H_{15}N_4O$ $[M + H]^+$ 267.1246, found 267.1262.



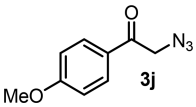
3i

*Phenacyl Azide (**3i**).* To a stirred solution of phenacyl bromide (1.50 g, 7.54 mmol) in DMSO (38 mL, 0.2 M) at ambient temperature was added sodium azide (1.20 g, 18.8 mmol, 2.5 equiv). After 15 min, the resulting mixture was poured into water with ice and the mixture was extracted twice with ether. The organic layer was washed with water and brine. The combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 5/1) gave 1.14 g of **3i** (94%): pale yellow oil; R_f value 0.53 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{max} 2104, 1697, 1218 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (dd, 2H, J = 8.0, 1.5 Hz), 7.65−7.62 (m, 1H), 7.50 (dd, 2H, J = 8.0, 8.0 Hz), 4.58 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 134.2, 134.1, 129.0, 127.9, 54.8; HRMS (CI) calcd for $C_8H_8N_3O$ $[M + H]^+$ 162.0667, found 162.0675.



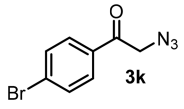
3j-1

*2-Bromo-1-(4-methoxyphenyl)ethan-1-one (**3j-1**).*[36] To a stirred solution of 4′-methoxyacetophenone (750.7 mg, 5.0 mmol) in 1,4-dioxane (8.2 mL, 0.6 M) was added bromine (0.28 mL, 5.45 mmol, 1.09 equiv) dissolved in ether (6.6 mL), and the mixture was heated up to 40 °C. After 2 h, the resulting mixture was cooled to room temperature and was washed five times with water. Then, the organic layer was dried over sodium sulfate. Concentration to obtain the crude solid material, which was recrystallized from ether, gave 329 mg of **3j-1** (29%): colorless crystal; R_f value 0.50 (hexane/ethyl acetate = 2/1); mp 70−71 °C; IR (NaCl, neat) ν_{max} 1686, 1600, 1261, 1206, 1170, 1022 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, 2H, J = 8.5 Hz), 6.96 (d, 2H, J = 8.5 Hz), 4.40 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.0, 164.1, 131.4, 126.9, 114.0, 55.6, 30.7; LRMS (EI, M = $C_9H_9BrO_2$) m/z 230 (46%, M^+ for ^{81}Br), 228 (46, M^+ for ^{79}Br), 135 (100); HRMS (EI) calcd for $C_9H_9{}^{81}BrO_2$ (M^+) 229.9765, found 229.9767.



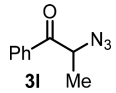
3j

*2-Azido-1-(4-methoxyphenyl)ethan-1-one (**3j**).* To a stirred solution of **3j-1** (267 mg, 1.16 mmol) in DMSO (5.8 mL, 0.2 M) at ambient temperature was added sodium azide (190 mg, 2.91 mmol, 2.5 equiv). After 20 min, the reaction was quenched with water, and the organic components were extracted three times with ether. The combined organic layer was washed with water and brine and was dried over sodium sulfate. Concentration to obtain crude solid material, which was recrystallized from hexane, gave 159 mg of **3j** (71%): pale yellow crystal; R_f value 0.60 (hexane/ethyl acetate = 1/1); mp 73 °C; IR (NaCl, neat) ν_{max} 2123, 1683, 1600, 1239, 1180, 1019, 945, 825 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, 2H, J = 9.0 Hz), 6.96 (d, 2H, J = 9.0 Hz), 4.51 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.6, 164.2, 130.3, 127.3, 114.1, 55.6, 54.5; LRMS (EI, M = $C_9H_9N_3O_2$) m/z 191 (2%, M^+), 135 (100), 92 (34), 77 (35); HRMS (EI) calcd for $C_9H_9N_3O_2$ (M^+) 191.0695, found 191.0692.



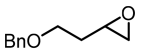
3k

*2-Azido-1-(4-bromophenyl)ethan-1-one (**3k**).*[37] To a stirred solution of 4-bromo phenacyl bromide (1.39 g, 5.0 mmol) in DMSO (25 mL, 0.2 M) at ambient temperature was added sodium azide (814 mg, 12.5 mmol, 2.5 equiv). After 10 min, the reaction was quenched with water, and the organic components were extracted three times with ether. The combined organic layer was washed with water and brine and was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 8/1) gave 1.05 g of **3k** (87%): pale yellow solid; R_f value 0.40 (hexane/ethyl acetate = 5/1); mp 79 °C; IR (KBr, disc) ν_{max} 2918, 2118, 1694, 1588, 1401, 1224, 1072, 1011, 815 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, 2H, J = 9.0 Hz), 7.65 (d, 2H, J = 9.0 Hz), 4.53 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.3, 133.0, 132.4, 129.5, 129.4, 54.8; HRMS (CI) calcd for $C_8H_7{}^{79}BrN_3O$ $[M + H]^+$ 239.9772, found 239.9767.



3l

*2-Azido-1-phenylpropan-1-one (**3l**).* To a stirred solution of 2-bromopropiophenone (0.76 mL, 5.0 mmol) in DMSO (25 mL, 0.2 M) at ambient temperature was added sodium azide (813 mg, 12.5 mmol, 2.5 equiv). After 0.5 h, the reaction was quenched with water, and the organic components were extracted three times with ether. The combined organic layer was washed with water and brine and was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave 757 mg of **3l** (87%): pale yellow oil; R_f value 0.40 (hexane/ethyl acetate = 5/1); IR (NaCl, neat) ν_{max} 2123, 2094, 1690, 1217, 964 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96−7.94 (m, 2H), 7.62 (t, 1H, J = 7.5 Hz), 7.51 (dd, 2H, J = 7.5, 7.5 Hz), 4.72 (q, 1H, J = 7.0 Hz), 1.57 (t, 3H, J = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.7, 134.2, 133.9, 128.9, 128.6, 58.3, 16.5; HRMS (CI) calcd for $C_9H_{10}N_3O$ $[M + H]^+$ 176.0824, found 176.0829.



3m-1

*2-(2-(Benzyloxy)ethyl)oxirane (**3m-1**).* To a stirred solution of D-aspartic acid (1.33 g, 10.0 mmol) in aqueous sulfuric acid (3.5 mL of conc sulfuric acid, 66 mmol, 6.6 equiv, diluted with 27 mL of water) at −5 °C was added potassium bromide (5.4 g, 45 mmol, 4.5 equiv) followed by the slow addition of an aqueous solution of sodium nitrite (1.2 g, 18 mmol, 1.8 equiv, dissolved in 2.4 mL of water). After 3 h at 0 °C, the brown mixture was extracted four times with ethyl acetate. The combined organic layer was dried over magnesium sulfate. Concentration in vacuo gave the brominated product (1.70 g) as a white solid. The compound was used without purification.

To a stirred solution of crude α-bromo carboxylic acid in THF (23 mL) was slowly added borane−THF complex (0.92 M in THF, 28.1 mL, 25.9 mmol, 3.0 equiv) at 0 °C. The white solution formed was stirred for 1 h at 0 °C, and then the cooling bath was removed to warm up to room temperature. After 2 h, the mixture was cooled again to 0 °C, and potassium carbonate (2.59 g) dissolved in water (10 mL) was slowly added. The suspension was stirred for 10 min at room temperature, and then the mixture was filtered through Celite; the precipitate was rinsed twice with diethyl ether. The obtained organic filtrate was washed with brine and was dried over magnesium sulfate. Concentration gave the crude bromohydrin product (1.17 g) as a pale yellow oil. The material was submitted to the next step without further purification.[38]

To suspension of sodium hydride (60% in material oil, 500 mg, 20.8 mmol, 3.0 equiv) in THF (10 mL) at −16 °C was added a solution of crude bromohydrin in THF (10 mL) dropwise. After 30 min, benzyl bromide (0.91 mL, 7.6 mmol, 1.1 equiv) and tetrabutylammonium iodide (2.56 g, 6.93 mmol, 1.0 equiv) were successively added to the reaction mixture at −10 °C, and the mixture was warmed up to room temperature. After an additional 3 h, water (10 mL) followed by saturated ammonium chloride aqueous solution (10 mL) was added carefully to the reaction mixture. After 1 h, the organic materials were extracted twice with ethyl acetate. The combined organic layer was dried over magnesium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 8/1 to 6/1) gave 692 mg of **3m-1** (39% for 3 steps). Although this is a chiral product, optical rotation value was not measured because its chirality

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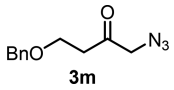
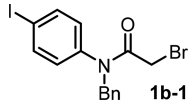
disappeared in next step. Compound **3m-1**: colorless oil; R_f value 0.60 (hexane/ethyl acetate = 5/1); IR (NaCl, neat) ν_{max} 2860, 2359, 1455, 1362, 1103, 833, 739, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.33 (m, 4H), 7.32−7.27 (m, 1H), 4.53 (s, 2H), 3.67−3.60 (m, 2H), 3.08 (ddt, 1H, J = 6.0, 4.5, 3.0 Hz), 2.79 (dd, 1H, J = 5.0, 4.5 Hz), 2.53 (dd, 1H, J = 5.0, 3.0 Hz), 1.92 (m, 1H), 1.78 (ddt, 1H, J = 14.0, 6.0, 6.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 128.4, 127.6, 73.1, 67.0, 50.1, 47.1, 32.9; HRMS (CI) calcd for $C_{11}H_{15}O_2$ $[M + H]^+$ 179.1072, found 179.1076.



3m

*1-Azido-4-(benzyloxy)butan-2-one (**3m**).* To a stirred solution of **3m-1** (542 mg, 3.04 mmol) in methanol/water (10.9 mL, 8/1, 0.3 M) were added ammonium chloride (326 mg, 6.08 mmol, 2.0 equiv) and sodium azide (1.58 g, 24.3 mmol, 8.0 equiv) successively at room temperature. Then the reaction mixture was warmed to 40 °C. After 10 h, the resulting mixture was cooled to room temperature and then was diluted with water. The organic materials were extracted twice with ether. The combined organic layer was dried over magnesium sulfate. Concentration in vacuo gave crude azidohydrin (620 mg), which was submitted to the next step without further purification.

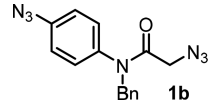
To a solution of oxalyl chloride (0.29 mL, 3.36 mmol, 1.2 equiv) in dichloromethane (1.7 mL) under a nitrogen atmosphere was added DMSO (0.40 mL, 5.6 mmol, 2.0 equiv), and the obtained crude material was dissolved in dichloromethane (7.6 mL, 0.4 M) dropwise at −78 °C. After 20 min, triethylamine (1.95 mL, 14.0 mmol, 5.0 equiv) was added slowly to the reaction mixture at the same temperature, and the mixture was warmed up to room temperature. After 30 min, the reaction mixture was diluted with dichloromethane and was washed with saturated aqueous ammonium chloride solution and twice with brine. The combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 2/1) gave 571 mg of **3m** (86% for 2 steps): colorless oil; R_f value 0.33 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{max} 2869, 2103, 1728, 1281, 1101, 740, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.34 (m, 2H), 7.31−7.29 (m, 3H), 4.51 (s, 2H), 4.00 (s, 2H), 3.76 (t, 2H, J = 6.0 Hz), 2.70 (t, 2H, J = 5.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.1, 137.6, 128.5, 127.8, 127.7, 73.3, 64.9, 58.1, 40.4; HRMS (CI) calcd for $C_{11}H_{14}N_3O_2$ $[M + H]^+$ 220.1086, found 220.1086.



1b-1

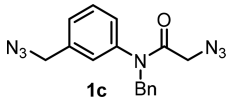
*N-Benzyl-2-bromo-N-(4-iodophenyl)acetamide (**1b-1**).* To a stirred solution of 4-iodoaniline (1.09 g, 5.0 mmol) in methanol (8.3 mL, 0.6 M) was added benzaldehyde (0.51 mL, 5.0 mmol, 1.0 equiv) at room temperature. After 0.5 h, the mixture was cooled to 0 °C. Sodium borohydride (631 mg, 15.0 mmol, 3.0 equiv) was added to the mixture carefully, and then the mixture was warmed up to room temperature. After 12 h, the resulting mixture was poured into a saturated aqueous sodium bicarbonate solution. The organic components were extracted three times with ethyl acetate and were washed with brine. The collected organic layer was dried over sodium sulfate. Concentration in vacuo gave *N*-benzyl-4-iodoaniline (1.06 g) as a crude material, which was submitted to the next step without further purification.

To a stirred solution of the crude amine (1.06 g) in dichloromethane (30.0 mL, 0.2 M) was added bromoacetyl bromide (0.34 mL, 3.92 mmol, 1.14 equiv) dissolved in dichloromethane (11.5 mL) at 0 °C. After the mixture stirred at room temperature for 2 h, the reaction mixture was quenched with a saturated aqueous sodium bicarbonate solution at 0 °C. The resulting mixture was washed with a saturated aqueous sodium bicarbonate solution, and the organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 5/1 with 5% toluene) gave 1.33 g of **1b-1** (62%): white solid; R_f value 0.27 (hexane/ethyl acetate = 5/1); mp 90−91 °C; IR (NaCl, neat) ν_{max} 1663, 1482, 1006 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, 2H, J = 8.5 Hz), 7.30−7.26 (m, 3H), 7.18−7.16 (m, 2H), 6.80 (d, 2H, J = 8.5 Hz), 4.86 (s, 2H), 3.65 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 140.8, 139.0, 136.2, 130.1, 128.9, 128.6, 127.8, 94.3, 53.5, 26.9; LRMS (EI, M = $C_{15}H_{13}BrINO$) m/z 431 (5%, M^+ of ^{81}Br), 429 (5, M^+ of ^{79}Br), 352 (2), 350 (100), 223 (26), 91 (77); HRMS (EI) calcd for $C_{15}H_{13}{}^{79}BrINO$ (M^+) 428.9225, found 428.9224.



1b

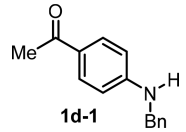
*2-Azido-N-(4-azidophenyl)-N-benzylacetamide (**1b**).* To a stirred solution of **1b-1** (215 mg, 0.50 mmol) in DMSO/water (3.3 mL, 5/1, 0.15 M) were added sodium azide (98.2 mg, 1.5 mmol, 3.0 equiv), copper(I) iodide (19.8 mg, 0.1 mmol, 0.2 equiv), sodium L-ascorbate (9.9 mg, 0.05 mmol, 0.1 equiv), and *N*,*N*′-dimethylethylenediamine (16.1 μL, 0.15 mmol, 0.3 equiv) successively at room temperature. After 12 h, the resulting mixture was poured into water, and the organic components were extracted three times with ether. The organic layer was washed with brine followed by drying over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 4/1) gave 138 mg of **1b** (90%): pale yellow oil; R_f value 0.57 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{max} 2103, 1672, 1505, 1279, 1256 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28−7.26 (m, 3H), 7.18−7.16 (m, 2H), 6.99 (d, 2H, J = 8.5 Hz), 6.92 (d, 2H, J = 8.5 Hz), 4.87 (s, 2H), 3.58 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 140.7, 136.7, 136.3, 129.7, 129.1, 128.6, 127.8, 120.3, 53.4, 50.8; LRMS (EI, M = $C_{15}H_{13}N_7O$) m/z 307 (7%, M^+), 279 (58), 118 (28), 91 (100); HRMS (EI) calcd for $C_{15}H_{13}N_7O$ (M^+) 307.1182, found 307.1174.



1c

*2-Azido-N-(3-(azidomethyl)phenyl)-N-benzylacetamide (**1c**).* To a stirred solution of **1c-1** (66.8 mg, 0.2 mmol) were added 4-toluenesulfonyl chloride (45.9 mg, 0.24 mmol, 1.2 equiv), 4-dimethylaminopyridine (3.2 mg, 0.02 mmol, 0.1 equiv) in dichloromethane (2.0 mL, 0.1 M), and triethylamine (37 μL, 0.26 mmol, 1.3 equiv) dropwise at 0 °C. After the mixture stirred at room temperature for 4 h, the reaction was quenched with water at 0 °C. The organic components were extracted twice with dichloromethane and then were washed with water and brine. The combined organic layer was dried over sodium sulfate. Concentration in vacuo gave crude tosylate (61.8 mg), which was submitted to the next step without purification. (Beware of residual dichloromethane; see also the caution statement above.)

To a stirred solution of the crude tosylate (61.8 mg) in DMSO (0.64 mL, 0.2 M) was added sodium azide (20.9 mg, 0.316 mmol, 2.5 equiv) at room temperature. After 1 h, the reaction was quenched with water, and the organic components were extracted 3 times with ether. The combined organic layer was washed with water and brine and then was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 8/1 to 4/1) gave 41.4 mg of **1c** (65% for 2 steps): pale yellow oil; R_f value 0.83 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2103, 1670, 1400, 1263, 1217, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, 1H, J = 8.0 Hz), 7.31−7.26 (m, 4H), 7.19−7.17 (m, 2H), 6.94−6.92 (m, 2H), 4.90 (s, 2H), 4.30 (s, 2H), 3.59 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 140.8, 137.6, 136.3, 130.5, 129.1, 128.6, 128.5, 128.1, 127.83, 127.78, 53.9, 53.4, 50.9; HRMS (CI) calcd for $C_{16}H_{16}N_7O$ $[M + H]^+$ 322.1416, found 322.1413.



1d-1

*1-(4-(Benzylamino)phenyl)ethan-1-one (**1d-1**).* To a stirred solution of 4′-aminoacetophenone (4.10 g, 30.3 mmol, 3.0 equiv) in

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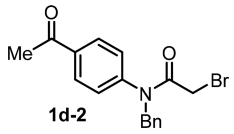
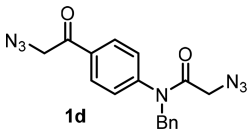
acetonitrile (20 mL, 1.5 M) were added potassium carbonate (2.09 g, 15.2 mmol, 1.5 equiv) and benzyl bromide (1.20 mL, 10.1 mmol) successively at room temperature. After 26 h at room temperature, the insoluble potassium carbonate was removed by filtration through filter paper and was washed with ethyl acetate. The collected filtrate was concentrated and was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain 2.00 g of **1d-1** (88% based on benzyl bromide): orange solid; R_f value 0.60 (hexane/ethyl acetate = 1/1); mp 90.1−91.8 °C; IR (NaCl, neat) ν_{max} 3349, 1650, 1596, 1358, 1280, 1179 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, 2H, J = 8.5 Hz), 7.38−7.34 (m, 4H), 7.32−7.29 (m, 1H), 6.60 (d, 2H, J = 8.5 Hz), 4.63 (s, 1H), 4.41 (s, 2H), 2.49 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.4, 151.9, 138.2, 130.7, 128.8, 127.5, 127.3, 126.8, 111.5, 47.5, 26.0; LRMS (EI, M = $C_{15}H_{15}NO$) m/z 225 (M$^+$, 77%), 210 (62), 91 (100); HRMS (EI) calcd for $C_{15}H_{15}NO$ (M$^+$) 225.1154, found 225.1155.



1d-2

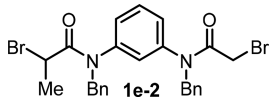
*N-(4-Acetylphenyl)-N-benzyl-2-bromoacetamide (**1d-2**).* To a stirred biphasic solution of **1d-1** (2.00 g, 8.86 mmol) in dichloromethane and water (125 mL, 1/4, 0.07 M) was added potassium carbonate (368 mg, 2.66 mmol, 0.2 equiv) at 0 °C. Then, bromoacetyl bromide (1.15 mL, 13.3 mmol, 1.5 equiv) dissolved in dichloromethane (45 mL) was added dropwise over 40 min at the same temperature. After 2 h, the mixture was warmed at room temperature. After 12 h, the reaction mixture was diluted with dichloromethane and was washed twice with water. The combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 2/1) gave 3.01 g of **1d-2** (98%): white solid; R_f value 0.50 (hexane/ethyl acetate = 1/1); mp 79−80 °C; IR (NaCl, neat) ν_{max} 1666, 1600, 1265 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, 2H, J = 9.0 Hz), 7.27−7.26 (m, 3H), 7.18−7.175 (m, 4H), 4.92 (s, 2H), 3.67 (s, 2H), 2.60 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8, 166.1, 145.2, 136.9, 136.1, 129.8, 128.8, 128.6, 128.4, 127.8, 53.5, 26.9, 26.7; HRMS (CI) calcd for $C_{17}H_{17}{}^{79}BrNO_2$ [M + H]$^+$ 346.0443, found 346.0439.



1d

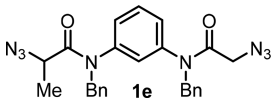
*2-Azido-N-(4-(2-azidoacetyl)phenyl)-N-benzylacetamide (**1d**).* To a stirred solution of *N*-benzyl-4-aminoacetophenone (175 mg, 0.500 mmol) in THF (6.4 mL) was added trimethylphenylammonium tribromide (207 mg, 0.550 mmol, 1.1 equiv) at 0 °C. After 12 h, the resulting precipitate was removed by filtration and was washed with ethyl acetate. Then the filtrate was washed with water and brine. The combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 2/1) gave 97.2 mg of dibromide (46%) as a colorless oil. Because the dibromide product was relatively unstable, this was soon submitted to the next step without collecting analytical data.

To a stirred solution of the dibromide (273 mg, 0.642 mmol) in DMSO (6.5 mL, 0.1 M) was added sodium azide (104 mg, 1.60 mmol, 2.5 equiv) at room temperature. After 1.5 h, the reaction was quenched with water. The organic components were extracted three times with ether and were washed with brine. The combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 2/1) gave 176 mg of **1d** (79%): pale yellow oil; R_f value 0.60 (hexane/EtOAc = 1/1); IR (NaCl, neat) ν_{max} 2105, 1672, 1600, 1215 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, 2H, J = 8.5 Hz), 7.29−7.26 (m, 3H), 7.17−7.13 (m, 4H), 4.93 (s, 2H), 4.52 (s, 2H), 3.62 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.1, 166.8, 145.2, 135.8, 134.0, 129.5, 128.6, 127.9, 54.8, 53.2, 50.8; HRMS (CI) calcd for $C_{17}H_{16}N_7O_2$ [M + H]$^+$ 350.1365, found 350.1360.



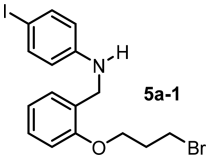
1e-2

*N-Benzyl-N-(3-(N-benzyl-2-bromoacetamido)phenyl)-2-bromopropanamide (**1e-2**).* To a stirred solution of the diamine **1e-1** (2.33 g, 8.08 mmol) in dichloromethane (77.0 mL, 0.083 M) was added bromoacetyl bromide (0.70 mL, 8.08 mmol, 1.0 equiv) dissolved in dichloromethane (10.0 mL) dropwise at 0 °C. After the mixture stirred at room temperature for 1 h, 2-bromopropionyl bromide (0.85 mL, 8.08 mmol, 1.0 equiv) dissolved in dichloromethane (10.0 mL) was added to the reaction mixture at 0 °C. After the mixture stirred at room temperature for 1 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution at 0 °C. The resulting mixture was washed with a saturated aqueous sodium bicarbonate solution and was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 3/1 to 2/1) gave 1.64 g of **1e-2** (37%): colorless viscous oil; R_f value 0.30 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{max} 1664, 1596, 1391, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, 1H, J = 8.0 Hz), 7.26−7.25 (m, 6H), 7.10−7.09 (m, 6H), 6.60 (br-s, 1H), 5.07−4.56 (m, 4H), 3.93 (br-s, 1H), 3.44 (s, 2H), 1.71 (br-d, 3H, J = 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 166.0, 141.7, 141.5, 136.1, 135.9, 130.8, 129.4, 128.87, 128.85, 128.75, 128.63, 128.58, 128.4, 127.95, 127.91, 53.33, 53.31, 38.9, 27.0, 21.6; LRMS (EI, M = $C_{25}H_{24}Br_2N_2O_2$) m/z 546 (1.3%, M$^+$ of ^{81}Br × 2), 544 (3, M$^+$ of ^{81}Br + ^{79}Br), 542 (1.3, M$^+$ of ^{79}Br × 2), 465 (85), 463 (85), 223 (25), 91 (100); HRMS (EI) calcd for $C_{25}H_{24}{}^{79}Br_2N_2O_2$ (M$^+$) 542.0205, found 542.0198.



1e

*2-Azido-N-(3-(2-azido-N-benzylacetamido)phenyl)-N-benzylpropanamide (**1e**).* To a stirred solution of **1e-1** (157 mg, 0.289 mmol) in DMSO (1.4 mL, 0.2 M) was added sodium azide (58.0 mg, 0.867 mmol, 2.5 equiv) at room temperature. After 1 h, the reaction was quenched with water, and the organic components were extracted three times with ether. The organic layer was washed with water and brine. The combined organic layer was then dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 2/1) gave 129 mg of **1e** (95%): white solid; R_f value 0.30 (hexane/ethyl acetate = 3/1); mp 104−105 °C; IR (NaCl, neat) ν_{max} 2105, 1667, 1397, 1235, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, 1H, J = 8.0 Hz), 7.28−7.25 (m, 5H), 7.10−7.01 (m, 7H), 6.31 (s, 1H), 4.91−4.71 (br, 4H), 3.22−3.15 (m, 3H), 1.30 (br-d, 3H, J = 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 166.8, 141.6, 141.0, 136.0, 135.8, 131.3, 129.4, 129.0, 128.9, 128.7, 128.6, 128.5, 128.1, 128.0, 54.0, 53.1, 53.0, 50.7, 16.2; HRMS (CI) calcd for $C_{25}H_{25}N_8O_2$ [M + H]$^+$ 469.2100, found 469.2095.



5a-1

*N-(2-(3-Bromopropoxy)benzyl)-4-iodoaniline (**5a-1**).* To a stirred solution of salicylaldehyde (1.23 g, 10 mmol) and potassium carbonate (2.77 g, 20 mmol, 2.0 equiv) in DMF (29 mL, 0.34 M) was added 1,3-dibromopropane (4.1 mL, 40 mmol, 4.0 equiv) at 0 °C. After 24 h at room temperature, the resulting mixture was diluted with ethyl acetate and was washed with water, 1 N HCl (twice), a saturated aqueous sodium bicarbonate solution, and brine. The combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane elution to hexane with 12% ethyl acetate) gave 1.86 g of 2(3-bromopropoxy)benzaldehyde (76%). This product was soon submitted to the next step without collecting analytical data.

To a stirred solution of 4-iodoaniline (1.36 g, 6.23 mmol) and the synthesized aldehyde above (1.82 g, 7.48 mmol, 1.2 equiv) in ethanol (31 mL, 0.2 M) was added acetic acid (0.43 mL, 7.48 mmol, 1.2 equiv)

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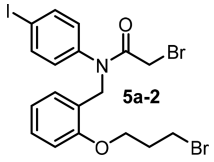
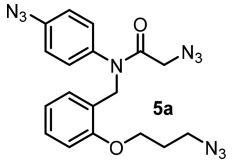
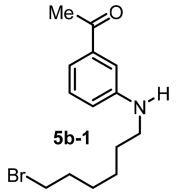
at room temperature. After 1 h, sodium cyanoborohydride (620 mg, 9.35 mmol, 1.5 equiv) was added to the reaction mixture at 0 °C. After the mixture stirred at room temperature for 13 h, the resulting mixture was poured into a saturated aqueous sodium bicarbonate solution. The organic components were extracted twice with ether and were washed with brine. The combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 5/1 with 2% trimethylamine) gave 2.71 g of **5a-1** (97%): white oil; R_f value 0.67 (hexane/ethyl acetate = 2/1); IR (NaCl, neat) ν_{max} 3418, 1589, 1434, 1454, 1238, 811, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.39 (m, 2H), 7.28−7.24 (m, 2H), 6.92 (dd, 2H, J = 12.5, 7.5 Hz), 6.43 (d, 2H, J = 9.0 Hz), 4.30 (s, 2H), 4.17 (t, 2H, J = 5.5 Hz), 4.13 (br-s, 1H), 3.58 (t, 2H, J = 6.5 Hz), 2.33 (tt, 2H, J = 6.5, 6.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 147.5, 137.7, 128.9, 128.6, 126.6, 120.8, 115.3, 111.2, 78.2, 65.1, 43.4, 32.0, 30.1; LRMS (EI, M = $C_{16}H_{17}BrINO$) m/z 447 (99%, M^+ of ^{81}Br), 445 (100, M^+ of ^{79}Br), 229 (60), 227 (61) 107 (60), 91 (34); HRMS (EI) calcd for $C_{16}H_{17}{}^{79}BrINO$ (M^+) 444.9538, found 444.9536.



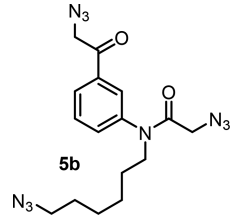
*2-Bromo-N-(2-(3-bromopropoxy)benzyl)-N-(4-iodophenyl)-acetamide (**5a-2**).* To a stirred solution of the **5a-1** (2.57 g, 5.76 mmol) in dichloromethane (49 mL) was added bromoacetyl bromide (0.57 mL, 6.57 mmol, 1.14 equiv) dissolved in dichloromethane (20 mL) at 0 °C. After the mixture stirred at room temperature for 1 h, the reaction was quenched with saturated aqueous sodium bicarbonate at 0 °C. The resulting mixture was washed with a saturated aqueous sodium bicarbonate solution. The combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane elution to hexane with 14% to 20% to 23% ethyl acetate) gave 3.28 g of **5a-2** (quant): colorless oil; R_f value 0.33 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{max} 1664, 1483, 1244, 1005, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, 2H, J = 8.5 Hz), 7.22 (dd, 1H, J = 8.5, 8.0 Hz), 7.17 (d, 1H, J = 7.5 Hz), 6.87 (t, 1H, J = 7.5 Hz), 6.82−6.80 (m, 3H), 4.93 (s, 2H), 3.96 (t, 2H, J = 5.5 Hz), 3.63 (s, 2H), 3.47 (t, 2H, J = 6.5 Hz), 2.14 (tt, 2H, J = 6.5, 5.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 156.6, 140.9, 138.7, 131.1, 130.2, 129.3, 124.1, 120.8, 111.1, 94.1, 65.1, 48.0, 32.0, 30.2, 27.0; LRMS (EI, M = $C_{18}H_{18}Br_2INO_2$) m/z 569 (0.4%, M^+ of $^{81}Br \times 2$), 567 (0.8, M^+ of ^{81}Br + ^{79}Br), 565 (0.4, M^+ of $^{79}Br \times 2$), 488 (99), 486 (100), 229 (39), 227 (40), 107 (38); HRMS (EI) calcd for $C_{18}H_{18}{}^{79}Br_2INO_2$ (M^+) 564.8749, found 564.8738.



*2-Azido-N-(4-azidophenyl)-N-(2-(3-azidopropoxy)benzyl)-acetamide (**5a**).* To a stirred solution of **5a-2** (3.23 g, 5.69 mmol) in DMSO/water (10/1, 56 mL, 0.1 M) were added sodium azide (1.66 g, 25.6 mmol, 4.5 equiv), copper(I) iodide (217 mg, 1.13 mmol, 0.2 equiv), sodium L-ascorbate (116 mg, 0.569 mmol, 0.1 equiv), and *N*,*N*′-dimethylenediamine (183 μL, 1.71 mmol, 0.3 equiv) successively at room temperature. After 16 h, the reaction mixture was poured into water and was extracted three times with ether. The combined organic layer was washed with brine and then was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 3/1) gave 2.03 g of **5a** (88%): colorless oil; R_f value 0.50 (hexane/ethyl acetate = 2/1); IR (NaCl, neat) ν_{max} 2101, 1671, 1505, 1279, 1246 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (ddd, 1H, J = 8.0, 7.5, 1.5 Hz), 7.15 (dd, 1H, J = 7.5, 1.5 Hz), 6.97−6.92 (m, 4H), 6.86 (dd, 1H, J = 7.5, 7.5 Hz), 6.79 (d, 1H, J = 8.0 Hz), 4.96 (s, 2H), 3.91 (t, 2H, J = 6.0 Hz), 3.56 (s, 2H), 3.40 (t, 2H, J = 6.5 Hz), 1.89 (tt, 2H, J = 6.5, 6.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 156.6, 140.5, 136.8, 131.2, 129.7, 129.3, 124.2, 120.8, 120.1, 111.1, 64.3, 50.9, 48.0, 47.7, 28.6; LRMS (EI, M = $C_{18}H_{18}N_{10}O_2$) m/z 406 (11%, M^+), 162 (81), 134 (100), 105 (83); HRMS (EI) calcd for $C_{18}H_{18}N_{10}O_2$ (M^+) 406.1614, found 406.1617.



*1-(3-((6-Bromohexyl)amino)phenyl)ethan-1-one (**5b-1**).* To a stirred solution of 3′-aminoacetophenone (1.35 g, 10.0 mmol) in acetonitrile (20 mL, 0.5 M) was added 1,6-dibromohexane (9.10 mL, 60.0 mmol, 6.0 equiv), and the mixture was heated to 90 °C. After 3 h, water (100 mL) was added to the mixture at room temperature for quenching the reaction. The organic components were extracted three times with ethyl acetate and was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane elution to hexane/ethyl acetate = 5/1) gave 1.19 g of **5b-1** (40%): yellow oil; R_f value 0.65 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 3386, 2932, 2856, 1677, 1603 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28−7.23 (m, 2H), 7.18 (br, 1H), 6.80 (dd, 1H, J = 7.0, 2.0, 2.0 Hz), 3.42 (t, 2H, J = 6.5 Hz), 3.16 (t, 2H, J = 7.0 Hz), 2.57 (s, 3H), 1.87 (tt, 2H, J = 7.5, 7.0 Hz), 1.65 (tt, 2H, J = 7.5, 6.5 Hz), 1.52−1.41 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 148.3, 138.1, 129.3, 117.8, 117.6, 111.4, 43.8, 33.8, 32.6, 29.1, 27.9, 26.8, 26.2; LRMS (EI, M = $C_{14}H_{20}BrNO$) m/z 299 (M^+ of ^{81}Br, 12%), 297 (M^+ of ^{79}Br, 12), 218 (9), 148 (100); HRMS (EI) calcd for $C_{14}H_{20}BrNO$ (M^+) 297.0728, found 297.0726.



*2-Azido-N-(3-(2-azidoacetyl)phenyl)-N-(6-azidohexyl)acetamide (**5b**).* To stirred solution of **5b-1** (2.13 g, 7.13 mmol) in dichloromethane (66 mL, 0.1 M) was added bromoacetyl bromide (0.71 mL, 8.13 mmol, 1.14 equiv) dissolved in dichloromethane (20 mL) at 0 °C. After the mixture stirred at room temperature for 1 h, the reaction mixture was quenched with a saturated aqueous sodium bicarbonate solution at 0 °C. The resulting mixture was washed with a saturated aqueous sodium bicarbonate solution, and the organic layer was dried over sodium sulfate. Concentration in vacuo gave crude amide (3.12 g), which was submitted to the next step without further purification.

To a solution of crude ketone in THF (92 mL, 0.08 M) under a nitrogen atmosphere was added trimethylphenylammonium bromide (2.95 g, 7.84 mmol, 1.1 equiv) at 0 °C. After 13 h, the reaction mixture was filtered through Celite, and then the filtrate was washed with water and brine. The organic layer was dried over sodium sulfate. Concentration in vacuo gave crude tribromide (4.4826 g), which was submitted to the next step.

To a solution of crude tribromide in DMSO (36 mL, 0.2 M) was added sodium azide (1.85 g, 28.5 mmol, 4.0 equiv) at room temperature. After 1 h, the reaction was quenched with water, and the organic components were extracted three times with ether. The combined organic layer was washed with water and brine and then was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (13% to 20% to 25% to 35% ethyl acetate in hexane) gave 1.94 g of **5b** (71% for 3 steps): colorless oil; R_f value 0.50 (hexane/EtOAc = 1/1); IR (NaCl, neat) ν_{max} 2935, 2858, 2103, 1670, 1438, 1263 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, 1H, J = 8.0 Hz), 7.76 (s, 1H), 7.62 (dd, 1H, J = 8.0, 8.0 Hz), 7.44 (d, 1H, J = 8.0 Hz), 4.58 (s, 2H), 3.73 (t, 2H, J = 7.5 Hz), 3.53 (s, 2H), 3.23 (t, 2H, J = 7.0 Hz), 1.57−1.50 (m, 4H), 1.40−1.30 (m, 4H); ^{13}C NMR

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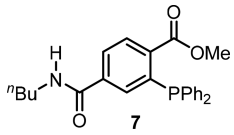
(126 MHz, $CDCl_3$) δ 192.1, 166.7, 141.6, 136.1, 133.5, 130.9, 128.0, 127.3, 55.0, 51.2, 50.8, 49.6, 28.6, 27.3, 26.3, 26.1; HRMS (CI) calcd for $C_{16}H_{21}N_{10}O_2$ $[M + H]^+$ 385.1849, found 385.1841.



7

*Methyl 4-(Butylcarbamoyl)-2-(diphenylphosphaneyl)benzoate (**7**).* To a stirred solution of 1-methyl-2-aminoterephthalate (976 mg, 5.0 mmol) in aq 4 M HCl (26.9 mL) was added $NaNO_2$ (380 mg, 5.5 mmol, 1.1 equiv) dissolved in water (9.8 mL) dropwise at 0 °C. After 30 min, potassium iodide (4.15 g, 25 mmol, 5.0 equiv) in water (33 mL, 0.15 M) cooled at −15 °C was slowly added to the reaction mixture at 0 °C. After the mixture was stirred at room temperature for 4 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution. The precipitated solid was collected by filtration and was washed with iced water. The obtained solid was recrystallized from methanol/water (1/1) to give 901 mg of 3-iodo-4-(methoxycarbonyl)benzoic acid (59%) as a yellow solid. Analytical data were identical to those reported.[29a,39]

In a flame-dried flask, obtained 3-iodo-4-(methoxycarbonyl)benzoic acid (980 mg, 2.91 mmol) was dissolved in methanol (29 mL, 0.1 M). To the stirred solution were added palladium(II) acetate (76.2 mg, 0.291 mmol, 0.1 equiv), triethylamine (0.82 mL, 5.82 mmol, 2.0 equiv), and diphenylphosphine (0.56 mL, 2.91 mmol, 1.0 equiv) at room temperature. The reaction mixture was stirred at reflux for 10 h, and then the resulting mixture was cooled down to room temperature. The crude material obtained after concentration in vacuo was dissolved with dichloromethane and was washed with water and aq 1 M HCl. After removal of organic solvent, the resulting material was dissolved by methanol and an equal volume of water was added to the solution. The solution was cooled to 4 °C for 2 h, and the resulting solid was collected by filtration to afford 663 mg of methyl 3-(diphenylphosphaneyl)-4-(methoxycarbonyl)benzoic acid[29a,39] as blown powder, which was submitted to the next step without further purification.

To a stirred solution of 3-(diphenylphosphaneyl)-4-(methoxycarbonyl)-benzoic acid (657 mg) in dichloromethane (80 mL) were added *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (427 mg, 2.22 mmol, 1.23 equiv), and 4-dimethylaminopyridine (22.1 mg, 0.186 mmol, 0.1 equiv) at room temperature. Then, a solution of *n*-butylamine (0.196 mL, 1.98 mmol, 1.1 equiv) in dichloromethane (10 mL) was added to the mixture. After 18 h, the reaction mixture was diluted with dichloromethane and was washed with 10% HCl (twice), saturated aqueous sodium bicarbonate (twice), water, and brine. The combined organic layer was dried over sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 3/1) gave 473 mg of **7** (39% from iodide for 2 steps): yellow solid; R_f value 0.6 (hexane/ethyl acetate = 1/1); mp 78−79 °C; IR (NaCl, neat) ν_{max} 3299, 2955, 1720, 1638, 1541, 1434, 1288 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, 1H, J = 8.5, 4.0 Hz), 7.80 (dd, 1H, J = 8.0, 1.5 Hz), 7.38−7.33 (m, 6H), 7.29−7.26 (m, 4H), 7.12 (dd, 1H, J = 3.5, 1.5 Hz), 5.70 (br-s, 1H), 3.75 (s, 3H), 3.31 (dd, 2H, J = 12.5, 6.5 Hz), 1.47−1.41 (m, 2H), 1.24 (ddt, 2H, J = 15.5, 7.5, 7.5 Hz), 0.90 (t, 3H, J = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5 (d, J = 2.4 Hz), 166.3, 141.5 (d, J = 28.8 Hz), 137.5, 137.2 (d, J = 10.7 Hz), 136.3 (d, J = 18.0 Hz), 133.8 (d, J = 20.4 Hz), 132.0, 131.0 (d, J = 2.4 Hz), 129.0, 128.6 (d, J = 7.2 Hz), 127.1, 52.3, 39.6, 31.2, 19.9, 13.7; ^{31}P NMR (202 MHz, benzene-d_6) δ −2.90; HRMS (ESI) calcd for $C_{25}H_{27}NO_3P$ $[M + H]^+$ 420.1729, found 420.1730.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02074.

^1H, ^{13}C, and ^1P NMR spectra and crystallographic data for compounds **4h**, **4i**′, and **2d** (PDF)

Crystal data for **4h** (CCDC no. 1839202) (CIF)

Crystal data for **2d** (CCDC no. 1839203) (CIF)

Crystal data for **4i**′ (CCDC no. 1839204) (CIF)

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Notes

The authors declare no competing financial interest.

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