HETEROCYCLES, Vol. 99, No. 2, 2019, pp. 1053 - 1072. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 10th September, 2018, Accepted, 5th October, 2018, Published online, 30th November, 2018
DOI: 10.3987/COM-18-S(F)72

# SYNTHESIS OF DIVERSE 3-AZIDO-5-(AZIDOMETHYL)BENZENE DERIVATIVES VIA FORMAL C–H AZIDATION AND FUNCTIONAL GROUP-SELECTIVE TRANSFORMATIONS

**Yoshitake Nishiyama, Yoshihiro Misawa, Yuki Hazama, Kazuhiro Oya, Suguru Yoshida,* and Takamitsu Hosoya***

Laboratory of Chemical Bioscience, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University (TMDU), 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan.
*E-mail: s-yoshida.cb@tmd.ac.jp, thosoya.cb@tmd.ac.jp

*This paper is dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday.*

**Abstract** – 3-Azido-5-(azidomethyl)benzene derivatives are useful compounds for preparing diverse bistriazole compounds and photoaffinity probes for target identification of bioactive compounds. To more easily synthesize a diverse range of diazido compounds, a facile method for synthesizing diazido compounds bearing a transformable functional group, such as iodo, bromo, methoxycarbonyl, or cyano group, was developed. This method is based on formal C–H azidation of 1,3-disubstituted benzenes via regioselective borylation followed by deborylative azidation, with subsequent transformations, such as that of a one-carbon unit on the benzene ring to an azidomethyl group. The functional groups of the diazido compounds were efficiently transformed to various connecting groups, including carboxy, (succinimidyloxy)carbonyl, hydroxymethyl, formyl, bromomethyl, tosylthiomethyl, ethynyl, diazoacetyl, bromoacetyl, boryl, hydroxy, aminocarbonyl, amino, and isothiocyanato groups, leaving the azido groups untouched. Several diazido building blocks were used to prepare diazido compounds by forming amide, thiourea, and sulfide bonds via conjugation at the connecting groups. These results show that the method described here would facilitate diazido probe syntheses and bistriazole library construction.

## INTRODUCTION

The azido group is a versatile functional group that has a wide field of application.[1] Organic azides are widely used as synthetic amine equivalents as well as precursors of nitrene species that are generated transiently by photoirradiation or heating (Figure 1A).[2] Moreover, click reactions[3] involving azide compounds, including copper-catalyzed azide–alkyne cycloaddition (CuAAC)[4] and strain-promoted azide–alkyne cycloaddition (SPAAC),[5] have enabled facile molecular conjugation via 1,2,3-triazole formation in various fields such as chemical biology, drug discovery, and materials science (Figure 1B).

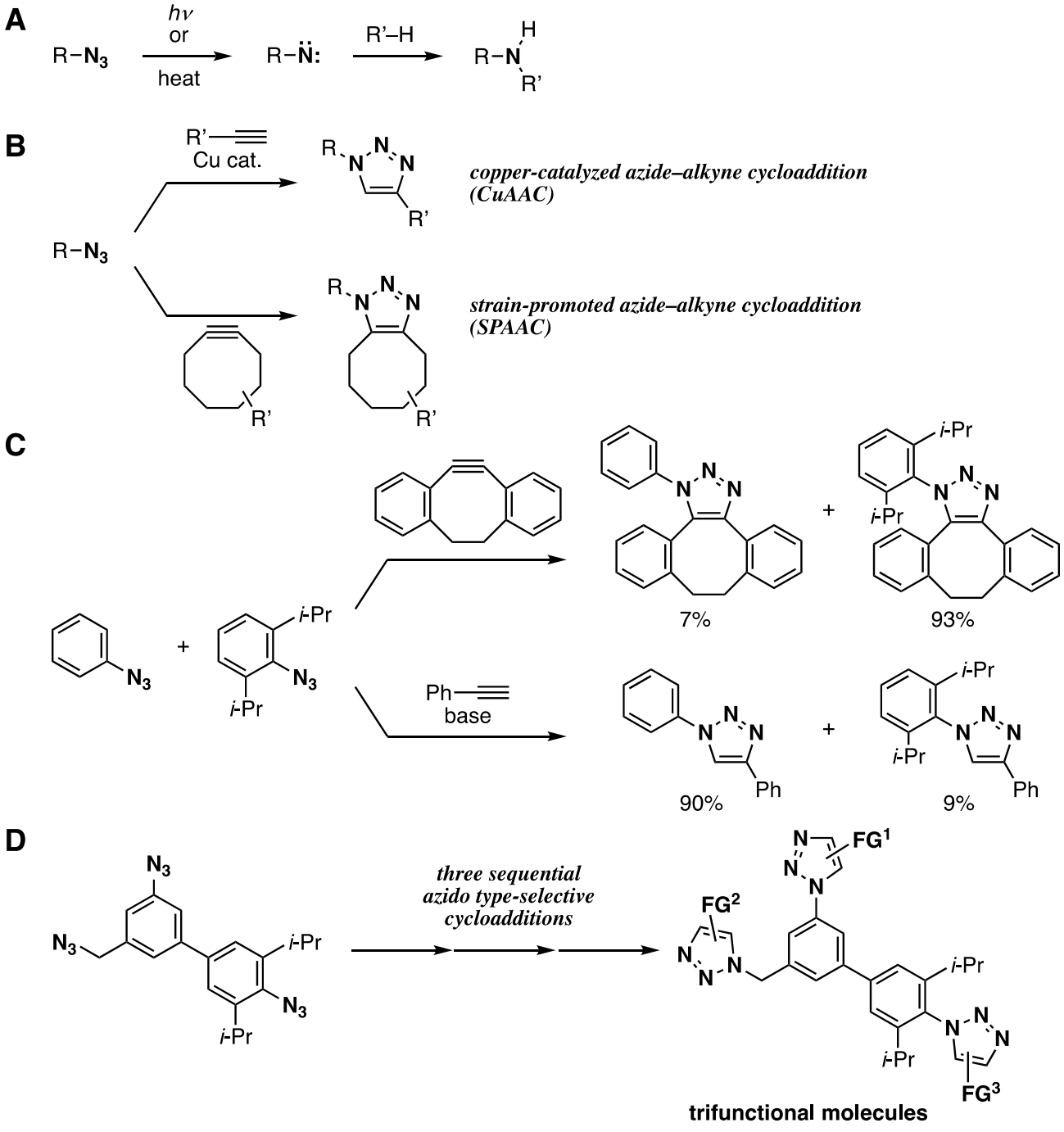



**Figure 1.** Azido as a versatile functional group

To enhance the synthetic utility of organic azides, we have been extensively studying on their reactivities and have found that they differ considerably depending on the type of azido group and reaction conditions, including azidophiles.[6] For instance, we previously discovered that sterically hindered 2,6-disubstituted aromatic azides exhibited significantly higher reactivity in SPAAC with dibenzo-fused cyclooctynes than phenyl azide, while the opposite result was observed for the cycloaddition with an acetylide (Figure 1C).[6a] Based on these unique characteristics of azides, we recently developed a facile method for synthesizing trifunctional molecules via three sequential azido-type-selective cycloadditions using a triazido platform molecule bearing three types of azido groups (Figure 1D).[6c]

We also found that aromatic azido groups exhibit considerably higher photoreactivity than the aliphatic azido groups. Based on this finding, we developed a convenient method for target identification of bioactive compounds via a two-step photoaffinity labeling[7] method employing a 3-azido-5-(azidomethyl)-benzene derivative as a probe (Figure 2).[8] The "diazido probe" was designed to bear aromatic and

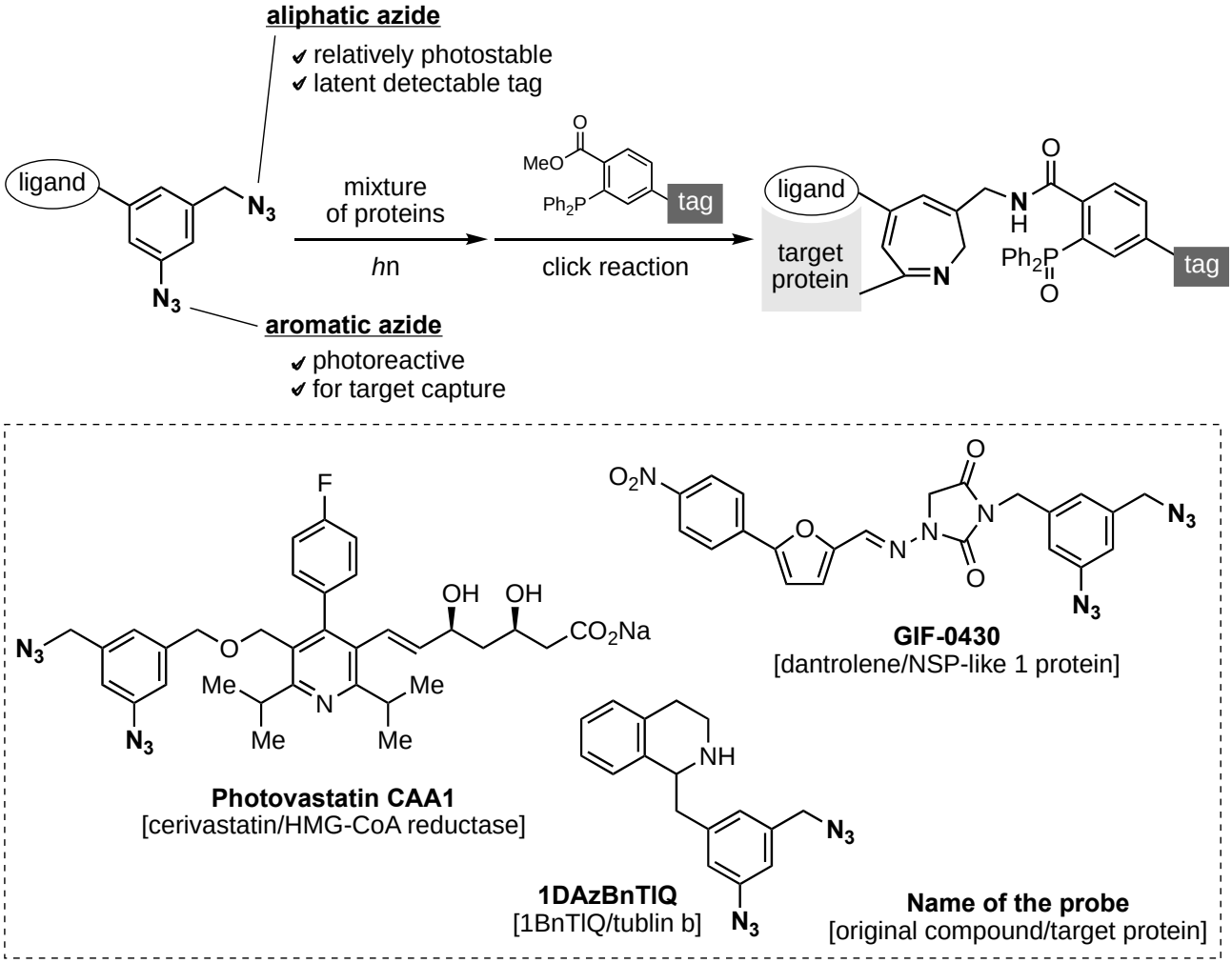


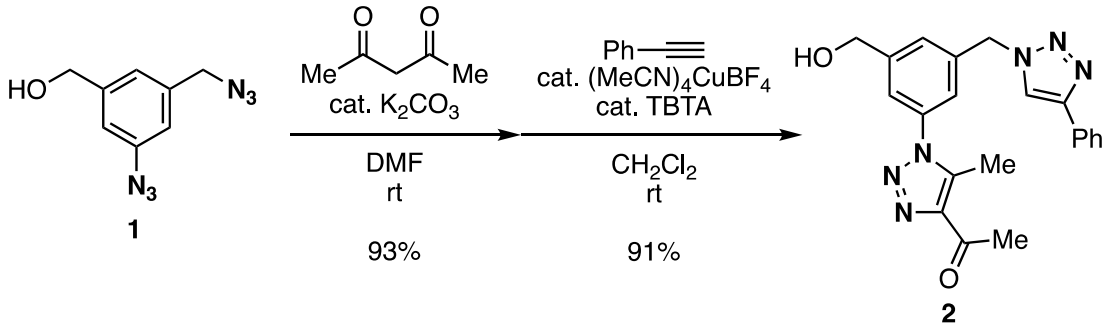

**Figure 2.** Photoaffinity labeling method employing diazido probes and examples of probe molecules

aliphatic azido groups having differing functions, a photoreactive group and a latent detectable group, respectively. After confirming that the probe was sufficiently bioactive compared with the original compound of interest, it was mixed with a biological sample, and the mixture was irradiated with 254 nm ultraviolet (UV) light to induce selective covalent bond formation between the target proteins and the probe at the highly photoreactive aromatic azido moiety. The remaining aliphatic azido group was employed as a tag to introduce a detectable group to the photolabeled proteins via azido-targeting click reactions including Staudinger–Bertozzi ligation.[9] This diazido probe strategy was successfully applied by our collaborators[8] and other groups[10] to identify unknown target proteins of bioactive compounds.

Based on recent advances in high throughput screening techniques that have allowed phenotypic assays using a massive chemical library, unknown target compounds are expected to increase. To address the increasing need for diazido probes, an efficient method for preparing various 3-azido-5-(azidomethyl)-benzene derivatives bearing a connecting group that can expedite probe synthesis is needed. For this purpose, we previously developed an efficient method for preparing several diazido building blocks, which was achieved by a regioselective C–H borylation of 1,3-disubstituted benzenes followed by deborylative azidation, with subsequent transformations including that of a one-carbon unit on the benzene ring to the azidomethyl group.[11] As diazido compounds are also potentially useful platform molecules for constructing a chemical library of bistriazole compounds, we launched a study to further increase the variety of diazido building blocks. In this paper, we report the details of our study on preparing diazido building blocks and their transformations.

## RESULTS AND DISCUSSION

The triazole skeleton is considered to be a bioisostere of amide structure, and many triazole derivatives have exhibited biological activities.[12] This suggests that a chemical library of bistriazole[13,14] could contain

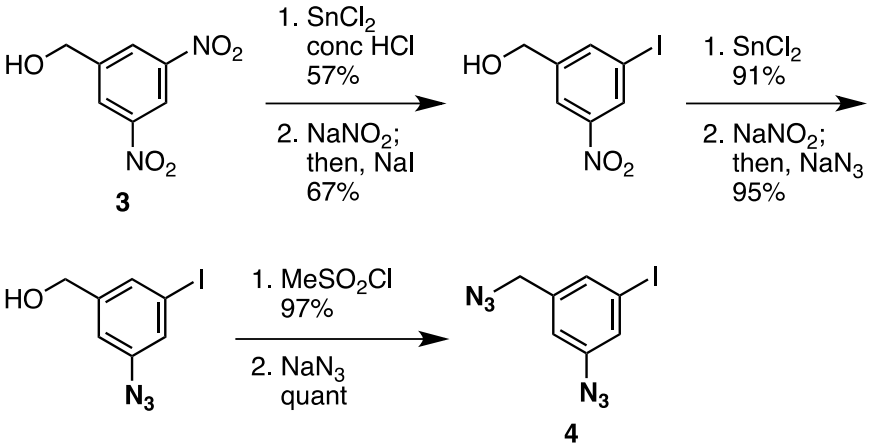



DMF = *N*,*N*-dimethylformamide, TBTA = tris[(1-benzyl-1*H*-1, 2, 3-triazol-4-yl)methyl]amine

**Scheme 1.** Bistriazole synthesis via azido-type-selective triazole formation

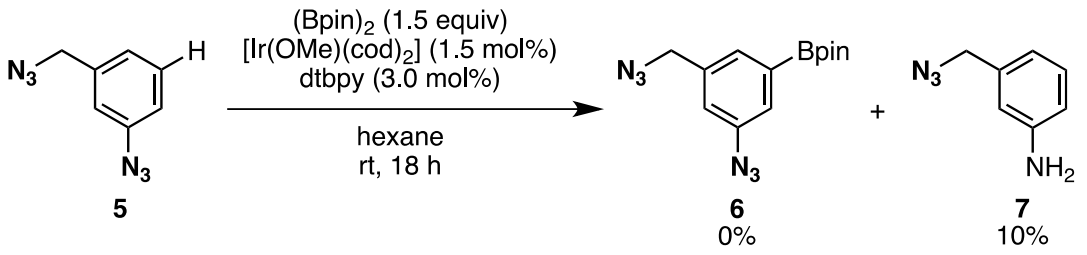
bioactive compounds. We considered that diverse bistriazoles could be easily prepared via sequential azido-type-selective triazole formation reactions of diazido compounds. Actually, treatment of 3-azido-5-(azidomethyl)benzyl alcohol (**1**) with acetylacetone under basic conditions,[15] followed by CuAAC with phenylacetylene selectively provided bistriazole **2** in high yield (Scheme 1). Changing the diazido building block and azidophiles could enable the rapid construction of a bistriazole library.

Since diazido compounds bearing two types of azido groups have proven useful not only for developing photoaffinity probes but also for synthesizing bistriazoles, we launched a study to efficiently synthesize various diazido compounds. Diazido building blocks were previously synthesized via their respective synthetic routes. For instance, we previously synthesized 1-azido-3-(azidomethyl)-5-iodobenzene (**4**) from 3,5-dinitrobenzyl alcohol (**3**) in six steps with an overall yield of about 30% (Scheme 2).[8d] Although this method was simple and reliable, a costly 1,3,5-trisubstituted benzene was used as a starting material, and a desymmetrization process distinguishing two nitro groups reduced the synthetic efficiency and the total yield.




**Scheme 2.** First-generation synthesis of diazido building block **4** bearing a connectable iodo group

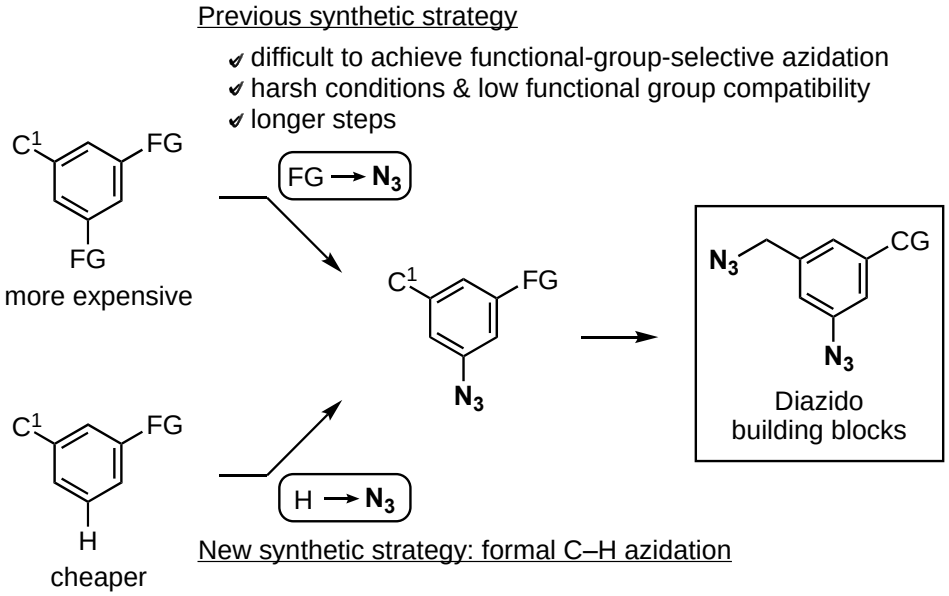
To prepare 3-azido-5-(azidomethyl)benzene derivatives such as **4** more easily and economically, we focused on iridium-catalyzed C–H borylation of 1,3-disubstituted benzenes,[16] which proceeds at the less hindered position of the benzene ring, and the installed boryl group can be transformed to other functional groups. These advantages inspired us to attempt the C–H borylation with readily synthesizable 1-azido-3-(azidomethyl)benzene (**5**) (Scheme 3). However, target compound **6** borylated at the 5-position was not obtained, and only a small amount of aniline **7** was detected.




pin = pinacolato, cod = 1,5-cyclooctadiene, dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridyl

**Scheme 3.** An attempt to synthesize a diazido building block bearing a boryl group by Ir-catalyzed C–H borylation of simple diazido compound **5**

Based on the result described above, we replaced the synthetic strategy with the new one involving the C–H azidation of 1,3-disubstituted benzenes bearing a one-carbon unit ($C^1$) and a functional group (FG) (Figure 3). Previous synthetic routes to diazido building blocks, such as **4** shown in Scheme 2, involve an inefficient functional-group-selective azidation of 1,3,5-trisubstituted benzenes, which is generally expensive and/or difficult to achieve. Conversely, C–H azidation, which we considered formally achievable by iridium-catalyzed borylation of inexpensive 1,3-disubstituted benzenes followed by deborylative azidation, was expected to be a more preferable route to 3,5-disubstituted phenyl azides, which can be converted to various diazido building blocks. As formal C–H azidation via iridium-catalyzed borylation is largely unexplored, we initially examined this transformation and its substrate scope in detail.

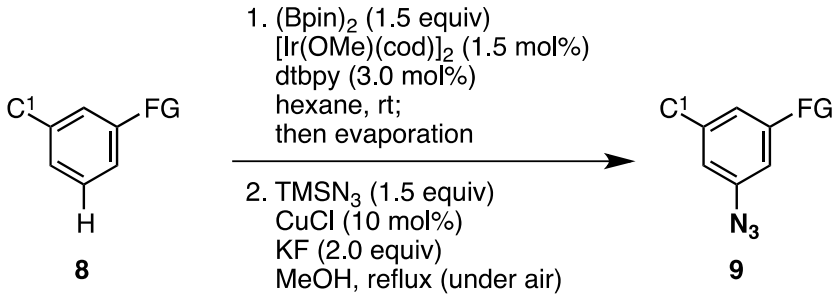



$C^1$ = one-carbon unit, FG = functional group, CG = connecting group

**Figure 3.** Previous and new synthetic routes to diazido building blocks

The desired formal C–H azidation was achieved by a sequence of iridium-catalyzed C–H borylation of 1,3-disubstituted benzenes and subsequent copper-catalyzed deborylazidation (Table 1). Although haloarenes generally react with transition metals by oxidative addition, the iridium-mediated C–H borylation of methyl 3-bromobenzoate (**8a**) and ethyl 3-iodobenzoate (**8b**) proceeded smoothly and regioselectively under the general conditions leaving bromo and iodo groups untouched,[16] enabling synthesis of a wide range of azido compounds via various conversions using these halogeno groups. After solvent removal, the resulting crude mixture containing the arylboronic acid pinacol ester was used in the subsequent copper-catalyzed deborylazidation[17] without further purification to give 1-azido-3-halo-benzoic acid esters **9a** and **9b** in high yields (entries 1 and 2). This one-pot procedure, which requires no purification of borylbenzene intermediates, is favorable because these types of arylboronates are normally difficult to purify by conventional silica gel column chromatography.[18] A key to efficiently achieving this two-step transformation is exposing the reaction mixture to air after the first borylation step. This procedure was performed to deactivate the iridium catalyst and prevent the reduction of azido group to the amino group as shown in Scheme 3. The optimized conditions were also applicable to the formal C–H azidation of other commercially available 1,3-disubstituted benzenes. For instance, methyl 3-methoxy-benzoate (**8c**) bearing a strongly electron-donating methoxy group also served as a good substrate to afford phenyl azide **9c** with no regioisomers (entry 3). The formal C–H azidation of trifluoromethyl- and

**Table 1.** Formal C–H azidation of 1,3-disubstituted benzenes



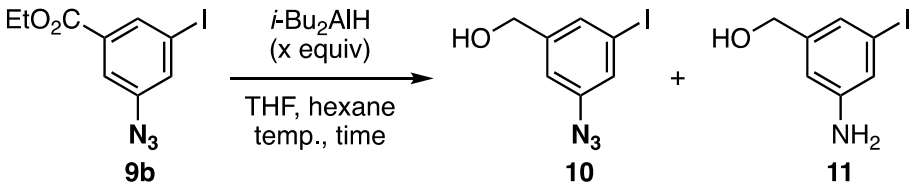

| entry | **8** | $C^1$ | FG | **9** | yield [%] |
|---|---|---|---|---|---|
| 1 | **8a** | $CO_2Me$ | Br | **9a** | 96 |
| 2 | **8b** | $CO_2Et$ | I | **9b** | 91 |
| 3 | **8c** | $CO_2Me$ | OMe | **9c** | quant |
| 4 | **8d** | $CO_2Me$ | $CF_3$ | **9d** | 93 |
| 5 | **8e** | $CO_2Me$ | CN | **9e** | 97 |
| 6 | **8f** | Me | $CO_2Me$ | **9f** | 95 |
| 7 | **8g** | Me | CN | **9g** | 70 |
| 8 | **8h** | $CO_2Et$ | STr | **9h** | 0 |
| 9 | **8i** | Me | $CH_2OH$ | **9i** | 0 |

TMS = trimethylsilyl, Tr = trityl

cyano-substituted benzoates **8d** and **8e** with two electron-deficient groups also proceeded smoothly to afford desired azides **9d** and **9e** in excellent yields, although electron-deficient arylboronic acids are frequently unstable (entries 4 and 5). Similarly, methyl 3-toluate (**8f**) and 3-tolunitrile (**8g**) afforded the corresponding 5-azidobenzene derivatives **9f** and **9g** in good yields (entries 6 and 7). Conversely, 1,3-disubstituted benzenes **8h** and **8i** bearing tritylthio and hydroxymethyl groups, respectively, were totally unsuitable substrates for the two-step formal C–H azidation (entries 8 and 9). The iridium-catalyzed borylation did not proceed efficiently in these cases.

With several 3,5-disubstituted phenyl azides bearing a $C^1$ unit and a transformable functional group in hand, we then explored the synthesis of diazido building blocks by transforming the $C^1$ unit to an azidomethyl group. As we had two types of 3,5-disubstituted phenyl azides with different $C^1$ units, those with ester moieties such as **9a** and **9b** and those with methyl groups such as **9f** and **9g**, we examined their transformations individually. To transform the ester moiety to the azidomethyl group, we believed that reducing the ester moiety to a hydroxymethyl group would be a suitable method, although there was a concern that the azido group might also be reduced. While treating ester **9b** with diisobutylaluminum hydride at −40 °C afforded the desired alcohol **10** in 73% yield, a considerable quantity of aniline **11** was also obtained together with the recovered starting material **9b** (Table 2, entry 1). After extensively screening the reaction conditions, alcohol **10** was selectively obtained in high yield by treating **9b** with 4.0 equivalents of diisobutylaluminum hydride at −78 °C for 3 h (entry 5).

**Table 2.** Screening of conditions for selective reduction of ester moiety of **9b** leaving other groups untouched

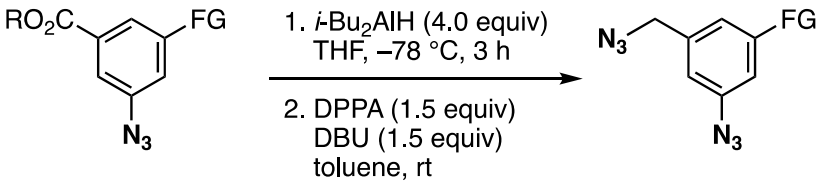



| entry | *i*-$Bu_2AlH$ (equiv) | temp. (°C) | time (h) | NMR yield (%) **9b** | **10** | **11** |
|---|---|---|---|---|---|---|
| 1 | 2.0 | –40 | 1 | 11 | 73 | 16 |
| 2 | 2.0 | –78 | 1 | 67 | 33 | 0 |
| 3 | 3.0 | –78 | 1 | 40 | 59 | 1 |
| 4 | 4.0 | –78 | 1 | 20 | 78 | 2 |
| 5 | 4.0 | –78 | 3 | 5 | 90 (83)[a] | 5 |

[a] Isolated yield in parentheses.

The resulting benzyl alcohol **10** was transformed to diazido compound **4** using unpurified alcohol under azidation conditions using diphenylphosphoryl azide (DPPA)[19,20] (Scheme 4). The overall yield of **4**[8d] from commercial **8b** via four steps was approximately 70%, which was significantly higher than that from

the previous six-step synthesis shown in Scheme 2. This two-step reduction–azidation sequence was also applicable to the synthesis of 1-azido-3-azidomethyl-5-bromobenzene (**12**) from ester **9a**.



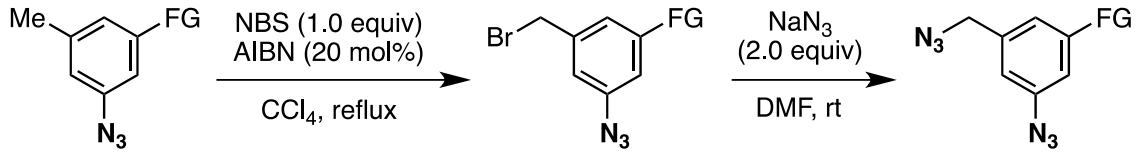

**9b** (FG = I, R = Et)
**9a** (FG = Br, R = Me)

**4** (FG = I), 77%, 2 steps
**12** (FG = Br), 63%, 2 steps

DPPA = diphenylphosphoryl azide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

**Scheme 4.** Transformation of the ester moiety to an azidomethyl group

To transform the methyl group to an azidomethyl group, benzylic bromination followed by azido substitution was effective. For instance, treatment of 3-azidotoluene derivative **9f** bearing an ester moiety at the 5-position with an equimolar amount of *N*-bromosuccinimide (NBS) afforded benzyl bromide **13** in a moderate yield, while some unreacted starting material **9f** was also recovered (Scheme 5). The subsequent substitution reaction of **13** with sodium azide afforded diazido building block **15**[10c,21] almost quantitatively. Diazido benzonitrile **16** was similarly prepared from 3-azido-5-cyanotoluene (**9g**) by the same two-step sequence.




**9f** (FG = $CO_2Me$)
**9g** (FG = CN)

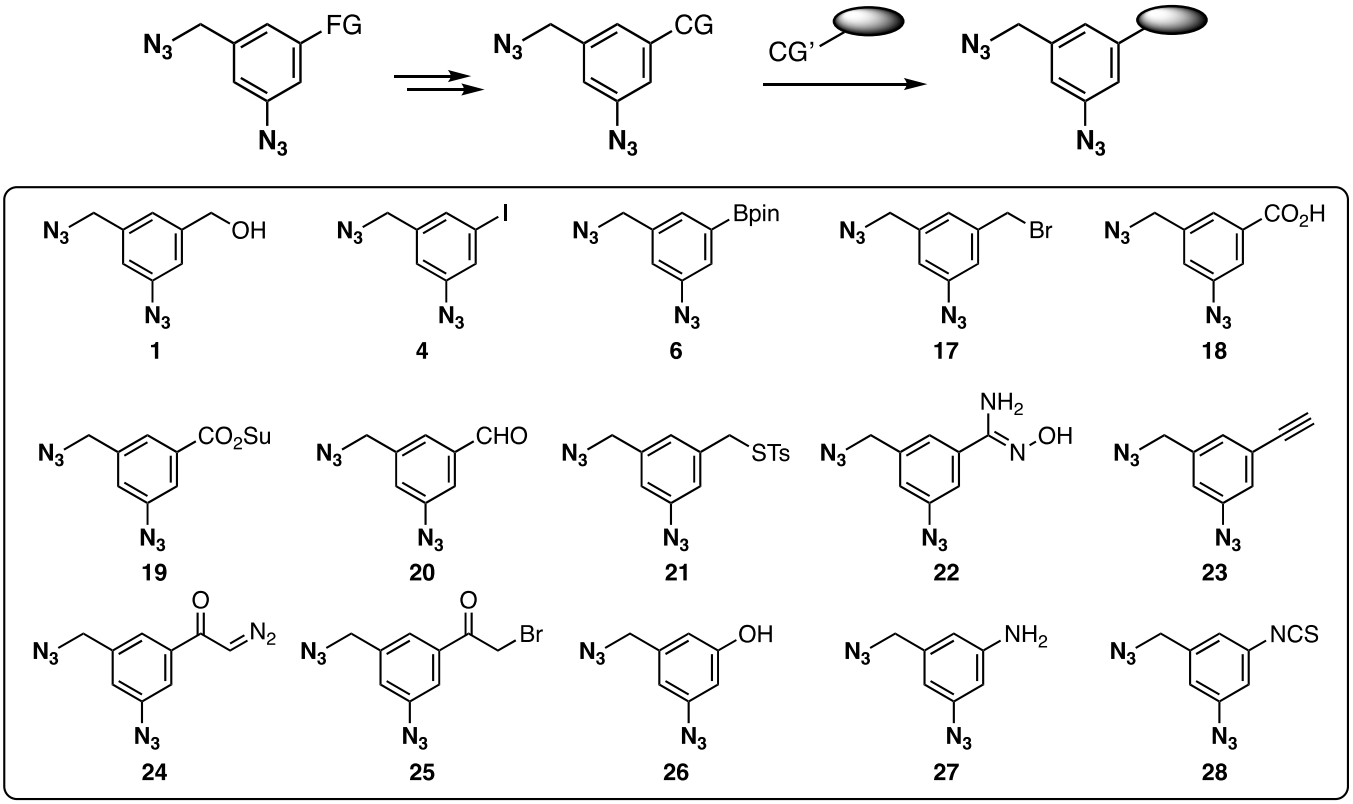
**13** (FG = $CO_2Me$), 55% (72% brsm)
**14** (FG = CN), 42% (60% brsm)

**15** (FG = $CO_2Me$), 98%
**16** (FG = CN), 99%

NBS = *N*-bromosuccinimide, AIBN = azobisisobutyronitrile, brsm = based on recovered starting material

**Scheme 5.** Transformation of the methyl group to an azidomethyl group

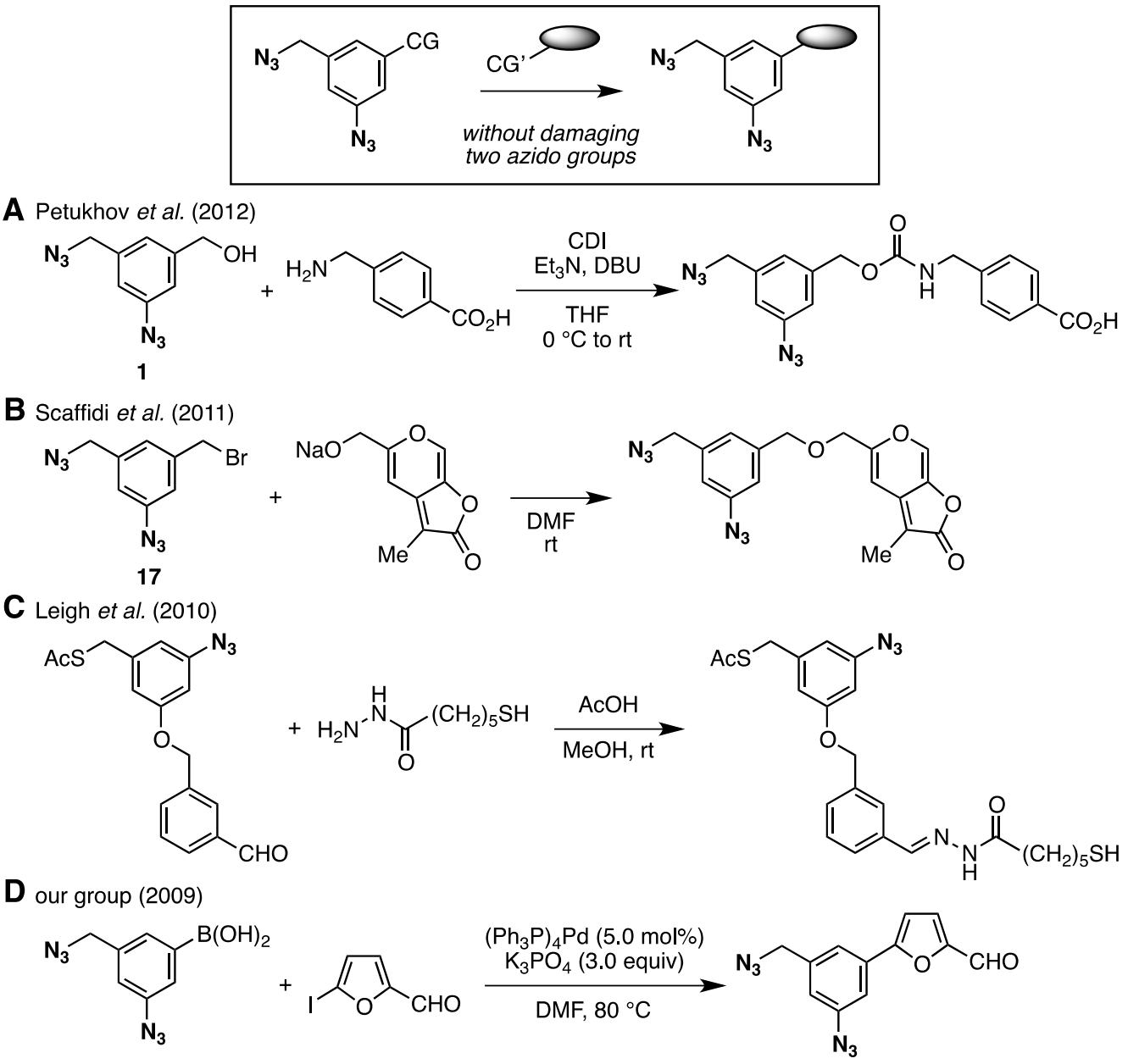
Since we successfully prepared several diazido compounds bearing different functional groups, such as iodo, methoxycarbonyl, and cyano groups, on a scale of more than several grams, we then aimed to increase the variety of diazido building blocks by transforming these above functional groups to other moieties that can be conveniently conjugated with other molecules. So far, we have obtained more than 15 types of diazido building blocks bearing connectable functional groups, which were prepared by functional group-selective transformations (Figure 4).




Su = *N*-hydroxysuccinimidyl, Ts = 4-toluenesulfonyl

**Figure 4.** Assorted diazido building blocks

Diazido photoaffinity probes have been prepared by conjugating the diazido building blocks with bioactive compounds or parts of their structures via connecting group-selective reactions (Scheme 6).[8,10] As well as the probe synthesis, many conjugation reactions involving azide compounds have been achieved while leaving the azido groups untouched. For example, diazido building blocks bearing a hydroxy group or a bromo group were used to synthesize complex diazido compounds by carbamate or ether formation (Schemes 6A and B).[10b,e] Conjugation between aldehydes and hydrazides bearing sensitive functional groups including azido groups was also achieved under mild conditions without damaging these functionalities (Scheme 6C).[22] As well as classical carbon–heteroatom bond forming reactions, we previously reported that the diazido building block was suitable for metal-catalyzed carbon–carbon bond forming reactions, such as Suzuki–Miyaura coupling reaction,[23] which allowed efficient synthesis of diazido compounds bearing biaryl structures (Scheme 6D).[8d] To facilitate the preparation of various diazido compounds, we increased the variety of diazido building blocks bearing a connecting group and demonstrated their utility by further derivatizations via several selective conjugation reactions.

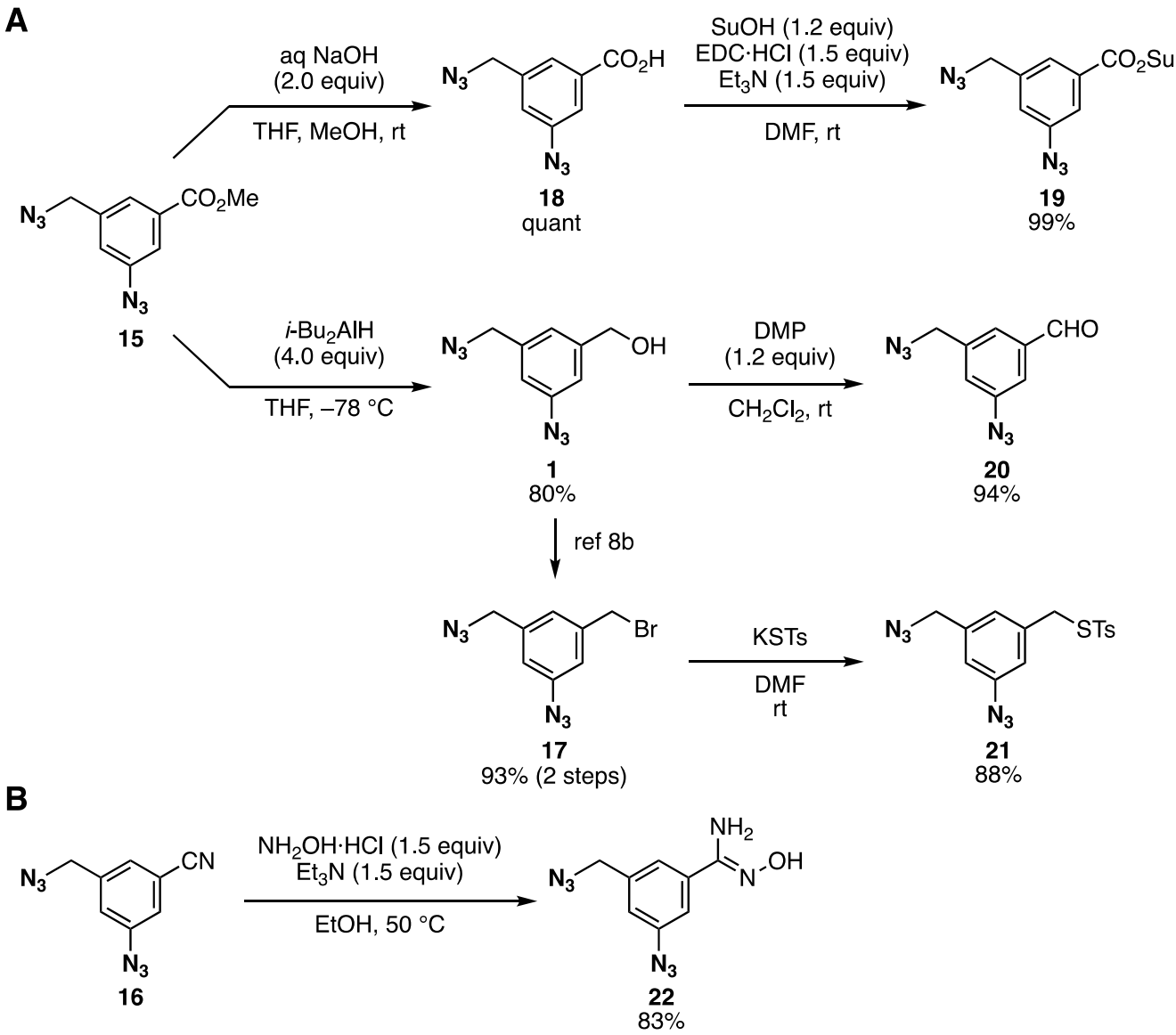



CDI = carbonyldiimidazole, Ac = acetyl

**Scheme 6.** Examples of conjugation reactions reported previously without damaging azido groups

We initially aimed to prepare diazido building blocks bearing a one-carbon connecting functional group via transformations of ester **15** and nitrile **16** (Scheme 7). Under the reported basic conditions employing sodium hydroxide, methyl ester **15** was smoothly hydrolyzed to quantitatively afford the corresponding carboxylic acid **18** without damaging the base-sensitive benzylic azido group (Scheme 7A).[10c] Condensation of carboxylic acid **18** with *N*-hydroxysuccinimide (SuOH) afforded activated ester **19**, which could be used for conjugation with bioactive compounds bearing hydroxy or amino groups. Treating ester **15** with 4.0 equivalents of diisobutylaluminum hydride at −78 °C gave benzyl alcohol **1**[8a,10c,21] in high yield, demonstrating that the azidomethyl group as well as the aromatic azido group was

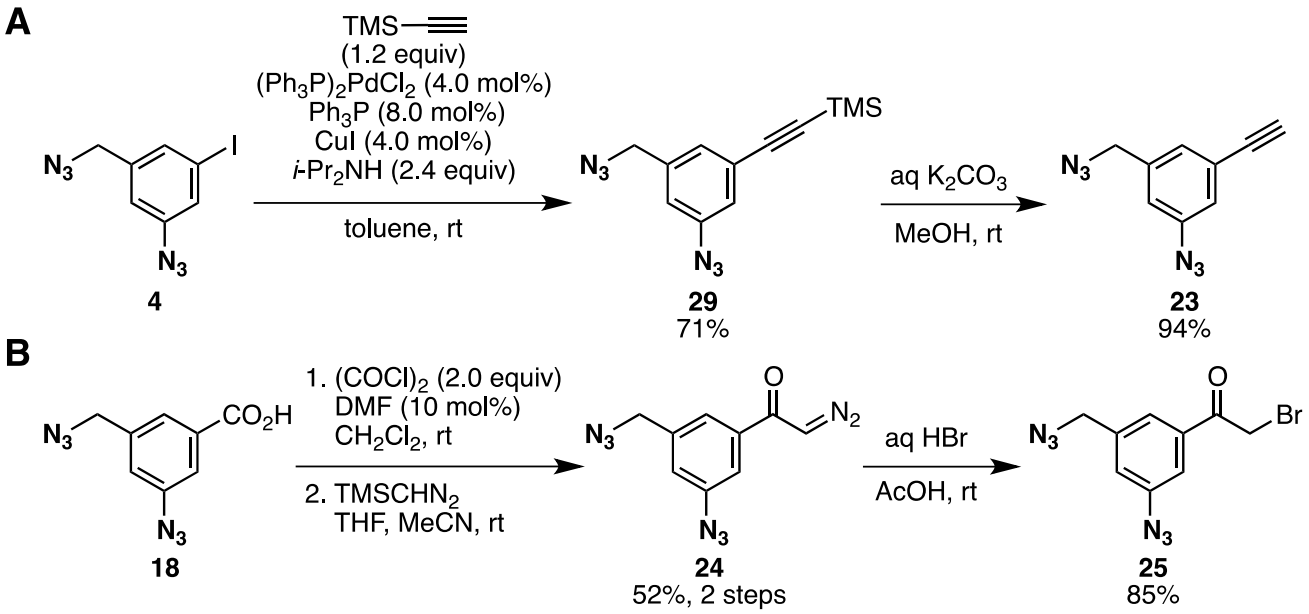
tolerated under these reduction conditions. The hydroxymethyl group of benzyl alcohol **1** was efficiently oxidized with Dess–Martin periodinane (DMP)[24] to afford diazido benzaldehyde **20**, which could be conjugated with amines, hydroxylamines, or hydrazines under mild conditions. Furthermore, as per our previous report, benzyl alcohol **1** was easily transformed to benzyl bromide **17**.[8b] Treating this bromide **17** with potassium 4-toluenethiosulfonate afforded thiosulfonate **21**, which can be subjected to electrophilic thiolation to prepare the diazido sulfide (vide infra).[25] Direct addition of hydroxylamine to nitrile **16** afforded the corresponding amidoxime **22**,[26] whose hydroxy group could be selectively *O*-acylated without acylation of the amino group (Scheme 7B).[27]




EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, DMP = Dess–Martin periodinane

**Scheme 7.** Synthesis of diazido building blocks bearing a $C^1$ connecting group

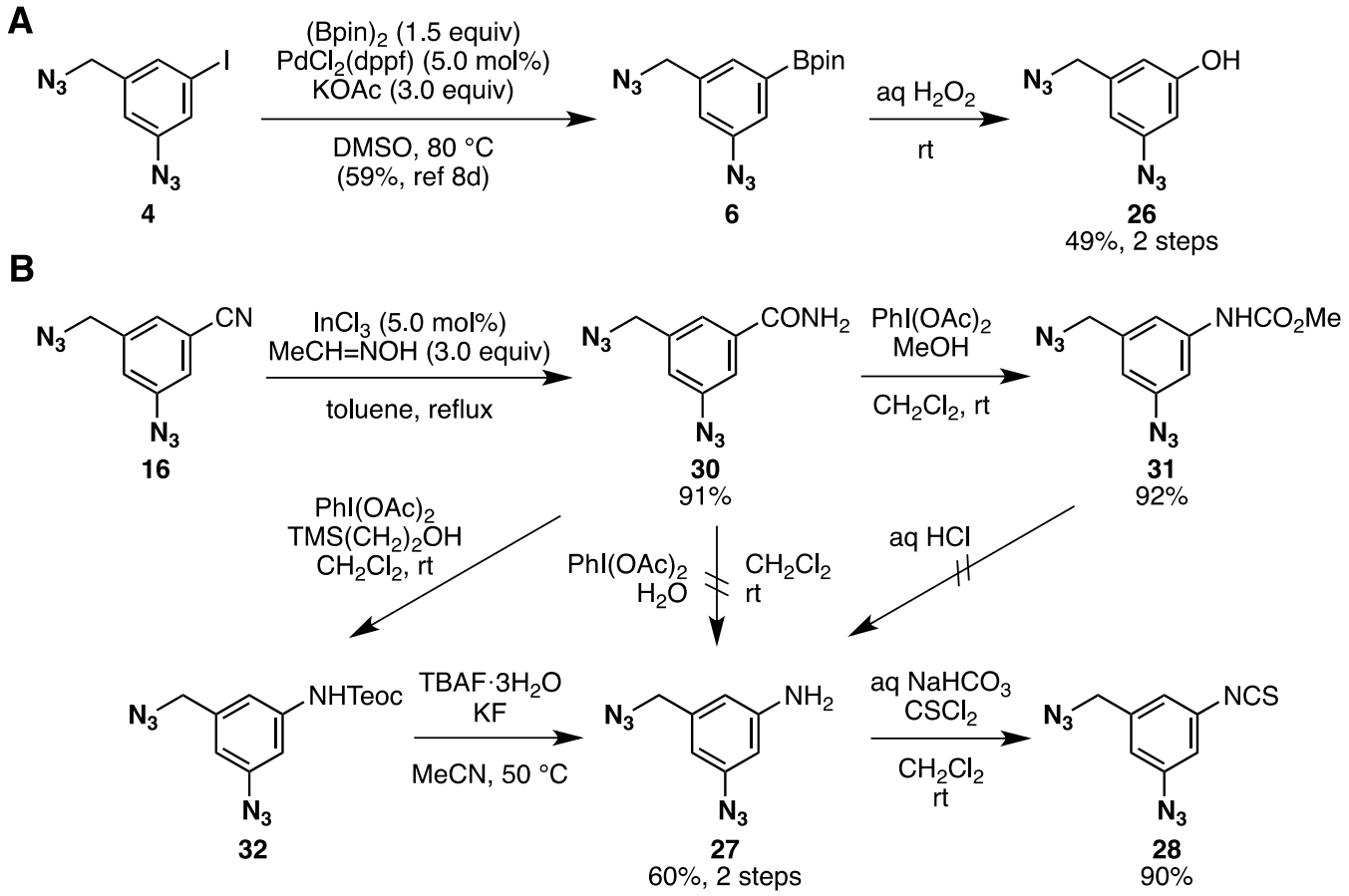
Aryl iodide **4** and benzoic acid **18** were used to synthesize diazido building blocks **23**–**25** bearing two-carbon connecting functional groups (Scheme 8). Sonogashira coupling reaction[28] between iodide **4** and trimethylsilylacetylene yielded alkyne **29**, whose protecting TMS group was smoothly removed under basic conditions to afford terminal alkyne **23** (Scheme 8A). Moreover, treating acid chloride prepared from carboxylic acid **18** with (trimethylsilyl)diazomethane afforded α-diazoketone **24** (Scheme 8B).[29] Further treatment of α-diazoketone **24** with hydrobromic acid in acetic acid afforded phenacyl bromide **25** via the selective transformation of the diazomethyl group among three types of 1,3-dipole groups.




**Scheme 8.** Synthesis of diazido building blocks bearing a $C^2$ connecting group

As well as the diazido building blocks bearing carbon substituents as connecting groups, we synthesized several heteroatom-substituted diazido building blocks (Scheme 9). For instance, we previously prepared boronic acid pinacol ester **6** by borylation[30] of iodide **4** and demonstrated that it could be used to synthesize various diazido-functionalized biaryl compounds by Suzuki–Miyaura coupling reaction (Schemes 9A and 6D).[8d] Oxidation of boronic ester **6** with aqueous hydrogen peroxide afforded the corresponding phenol **26**, which could be employed for alkylation or acylation with various electrophiles. Moreover, considering that aniline derivatives are frequently present in bioactive compounds, diazido building blocks bearing nitrogen functional groups such as aniline **27** and isothiocyanate **28** were prepared by transforming nitrile **16** (Scheme 9B). Although our initial attempt to hydrolyze nitrile **16** to amide **30** using a rhodium catalyst was unsuccessful, an indium catalyst promoted the desired hydrolysis, affording **30** in high yield.[31] We then attempted to prepare aniline **27** from amide **30** via modified Hofmann rearrangement using a hypervalent iodine reagent. While treating amide **30** with (diacetoxyiodo)benzene in the presence of methanol smoothly afforded methyl carbamate **31**,[32] the

reaction did not proceed in the presence of water, and the desired aniline **27** was not obtained. We therefore tried to prepare aniline **27** by removing the methoxycarbonyl group of **31** under acidic conditions; however, this attempt was also unsuccessful. To achieve this transformation, we synthesized 2-(trimethylsilyl)ethoxycarbonyl (Teoc)-protected aniline **32** by performing Hofmann rearrangement of amide **30** in the presence of 2-(trimethylsilyl)ethanol. The Teoc group of **32** was smoothly removed under milder conditions using tetrabutylammonium fluoride (TBAF) to afford the desired aniline **27**.[33] Treating aniline **27** with thiophosgene under basic conditions gave isothiocyanate **28** in high yield.[34]

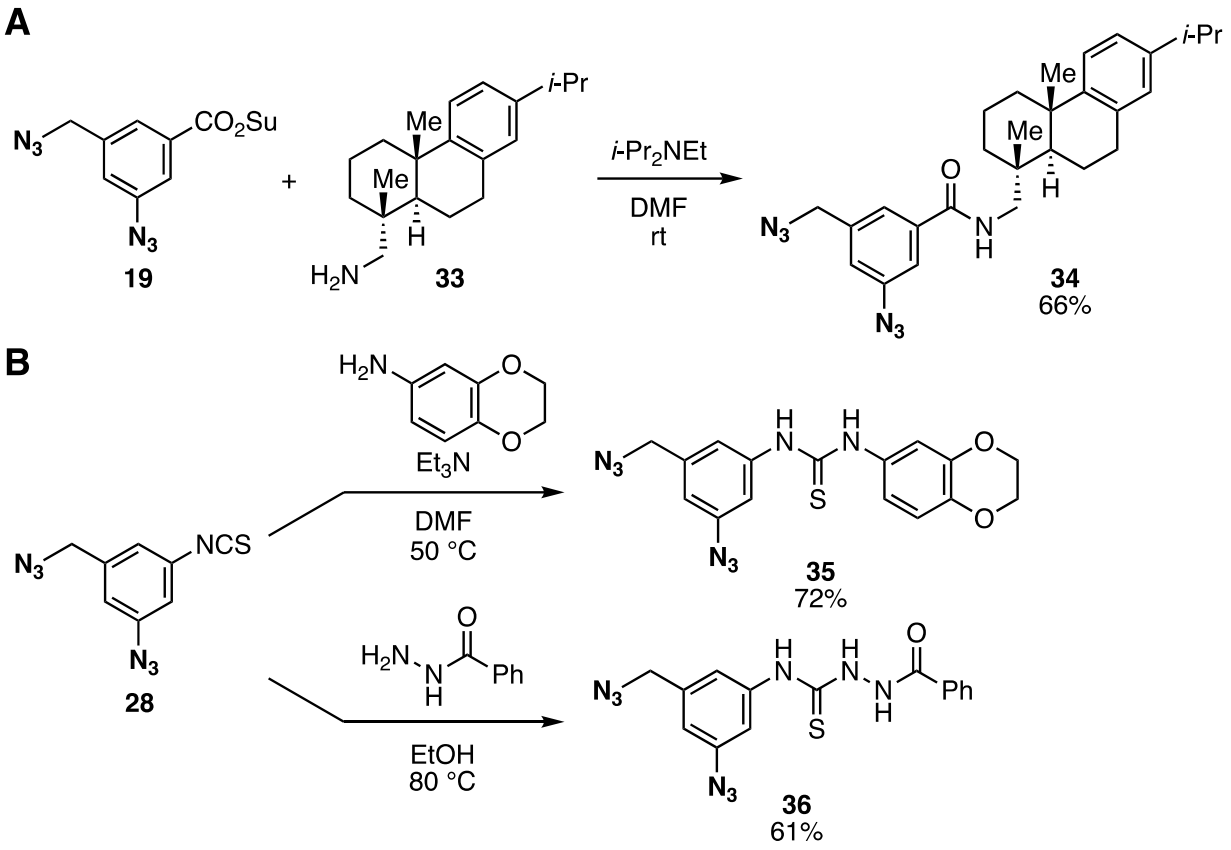



dppf = 1,1'-bis(diphenylphosphino)ferrocene, DMSO = dimethyl sulfoxide,
Teoc = 2-(trimethylsilyl)ethoxycarbonyl, TBAF = tetrabutylammonium fluoride

**Scheme 9.** Synthesis of diazido building blocks bearing a heteroatom on the benzene ring

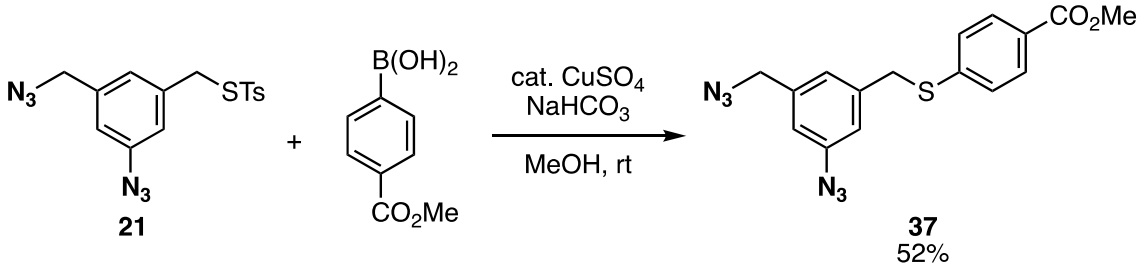
With diazido building blocks bearing various connecting groups in hand, we examined the suitability of several new ones for conjugation. We initially explored the diazido-functionalization of various compounds bearing an amino group using activated ester **19** and isothiocyanate **28** (Scheme 10). Treating dehydroabietylamine (**33**),[35] an inhibitor of pyruvate dehydrogenase kinase, with succinimidyl ester **19** in the presence of Hünig's base afforded diazido-functionalized dehydroabietylamine **34** (Scheme 10A).

Furthermore, isothiocyanate **28** reacted not only with aniline but also with hydrazide to afford the corresponding thiourea derivatives including **35** and **36** (Scheme 10B).




**Scheme 10.** Conjugation of various amines at the connecting groups of diazido building blocks

As well as the classical condensation, addition, and substitution reactions, diazido building blocks can be subjected to metal-catalyzed reactions, such as palladium-catalyzed Suzuki–Miyaura coupling reaction,[8d] significantly expanding the range of synthesizable diazido compounds. The use of thiosulfonate **21** in metal-catalyzed reactions has further increased the synthesizable diazido compounds containing sulfur functionalities. For instance, diazido-functionalized sulfide was easily prepared by applying the copper-catalyzed deborylthiolation reaction that we recently reported.[25] Thus, treating thiosulfonate **21** with 4-(methoxycarbonyl)phenylboronic acid in the presence of copper(II) catalyst and sodium bicarbonate afforded sulfide **37** (Scheme 11). Considering that azides are prone to degradation when exposed to thiols, diazido-functionalized thiosulfonate **21**, which can be stored for a long period of time, is a useful reagent for the synthesis of sulfur-containing diazido compounds.




**Scheme 11.** Copper-catalyzed synthesis of diazido-functionalized sulfide using thiosulfonate **37**

In conclusion, we have established a facile method for preparing diverse diazido compounds containing aliphatic and aromatic azido groups that show differing reactivities depending on the reaction conditions. Formal C–H azidation of inexpensive 1,3-disubstituted benzenes via a borylation–azidation sequence, followed by transformation of one-carbon units to azidomethyl group, afforded diazido building blocks bearing functional groups. These functional groups were transformed to various connecting groups without damaging the azido groups. Based on this diversity-oriented short-step synthesis, more than 15 diazido building blocks have been prepared and stocked, being always available for use. These diazido building blocks were successfully conjugated with various molecules via condensation, addition, and substitution reactions, as well as transition metal-catalyzed coupling reactions, leaving the azido groups untouched. These results show that this method aids the synthesis of diazido photoaffinity probes and construction of a bistriazole library.

## EXPERIMENTAL

Experimental procedures, characterization for new compounds including copies of NMR spectra (PDF) are available in the Supporting Information.

## ACKNOWLEDGEMENTS

This work was supported by Japan Agency for Medical Research and Development (AMED) under Grant Numbers JP18am0101098 (Platform Project for Supporting Drug Discovery and Life Science Research, BINDS) and JP18am0301024 (the Basic Science and Platform Technology Program for Innovative Biological Medicine); JSPS KAKENHI Grant Numbers JP15H03118 and JP18H02104 (B; T. H.), JP16H01133 and JP18H04386 (Middle Molecular Strategy; T. H.), JP17H06414 (Organelle Zone; T. H.), JP26350971 (C; S. Y.), and JP17K13266 (Young Scientist B; Y. N.); the Cooperative Research Project of Research Center for Biomedical Engineering; and the Naito Foundation (S. Y.).

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