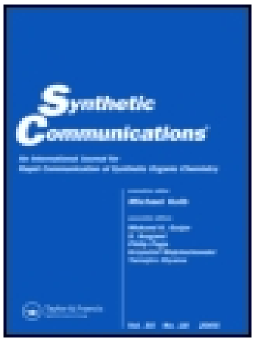

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Direct $AlCl_3$-catalyzed transformation of benzyl THP ethers and allyl benzyl ethers

Tien Tan Bui[a,b] and Hee-Kwon Kim[a,b]

[a]Department of Nuclear Medicine, Molecular Imaging & Therapeutic Medicine Research Center, Chonbuk National University Medical School and Hospital, Jeonju, Republic of Korea; [b]Research Institute of Clinical Medicine of Chonbuk National University-Biomedical Research Institute of Chonbuk National University Hospital, Jeonju, Republic of Korea

ABSTRACT

THP and allyl groups are frequently used for the protection of alcohols. In this study, novel direct transformations of benzyl THP ethers and allyl benzyl ethers, protected forms of alcohols, are reported. $TMSN_3$ and $AlCl_3$ were employed as key azide reagent and catalyst to perform direct conversion of benzyl THP ethers and allyl benzyl ethers to azido compounds. In addition, direct nucleophile additions of carbon nucleophiles to benzyl THP ethers and allyl benzyl ethers were successfully accomplished in the presence of catalytic $AlCl_3$. The results indicate that this novel method could be applied to various direct transformations of benzyl THP ethers and allyl benzyl ethers such as azidation, allylation, and alkynylation.

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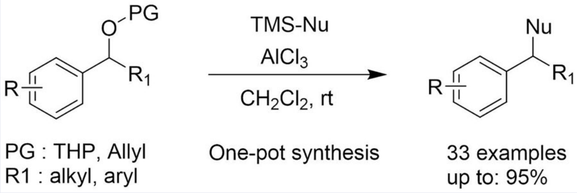
KEYWORDS
Allyl ethers; Aluminum(III) chloride; catalysts; DPM azides; THP ethers

GRAPHICAL ABSTRACT



Introduction

Alcohols are widely distributed moieties in organic chemistry, and various protecting groups for alcohols are employed to prevent the generation of by-products during organic procedures. In particular, tetrahydropyranyl (THP) and allyl groups are commonly utilized as protecting groups of alcohols. To achieve nucleophilic substitution of THP- and allyl- protected alcohols, several reaction steps are required: elimination of the protecting group and transformation to an active leaving group such as halide, triflate, and mesylate.[1–3] Thus, the development of an efficient direct transformation of

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CONTACT Hee-Kwon Kim ✉ hkkim717@jbnu.ac.kr Department of Nuclear Medicine, Molecular Imaging & Therapeutic Medicine Research Center, Chonbuk National University Medical School and Hospital, Jeonju, 54907, Republic of Korea; Research Institute of Clinical Medicine of Chonbuk National University-Biomedical Research Institute of Chonbuk National University Hospital, Jeonju, 54907, Republic of Korea.

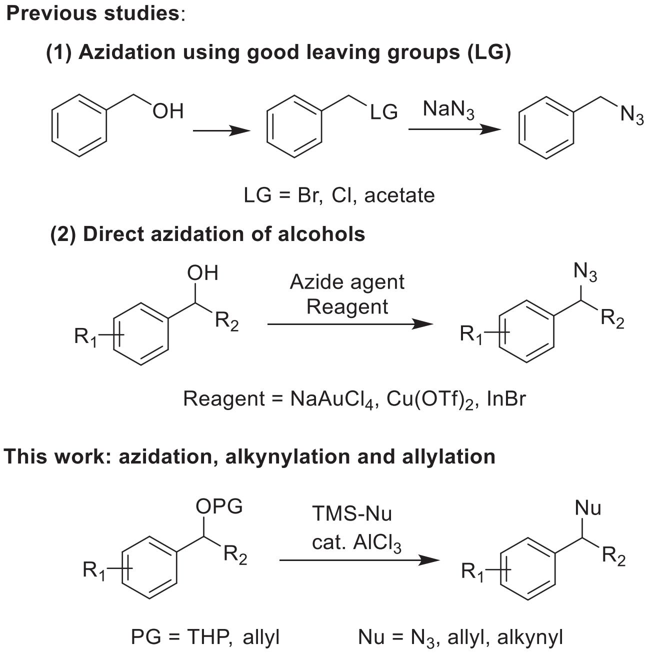
THP- and allyl-protected alcohols is an appealing approach with benefits including shortened reaction steps and a decrease of waste material.

Azides are identified as precious organic synthesis intermediates leading to nitrenes,[4] amines,[5,6] and heterocycles.[7,8] Furthermore, utilization of azides in click chemistry is an important protocol for the attachment of various biomarkers to macromolecules.[9,10] In particular, the formations of azides from benzhydryl alcohols were used for the synthesis of (diarylmethyl)amine precursors, which are components of commercial drugs such as meclizine[11] and levocetirizine.[12] In additions, azides also contribute important biological activity in some pharmaceuticals such as the HIV/AIDS drug AZT, known as zidovudine.[13] Therefore, various methods have been used for the preparation of azides.

The popular method to synthesize azides involves two separate steps: first, conversion of the hydroxyl group to a halogen[14] or acetal,[15] and then azide formation by a substitution reaction with sodium azide (NaN_3). However, these protocols have drawbacks such as the toxicity of sodium azide.[16] In addition, several methods for direct azidation from a free hydroxyl group using various reagents such as sodium tetrachloroaurate,[17] copper triflate,[18] and indium (III) bromide[19] have been reported. We were attracted to discover an efficient direct conversion of protected alcohols using a novel catalyst. Herein, we describe novel conversion of benzyl THP ethers and allyl benzyl ethers directly to azido compounds using a catalyst. Moreover, the direct alkynylation and allylation of benzyl THP ethers and allyl benzyl ethers could also be achieved using this catalytic procedure (Scheme 1).

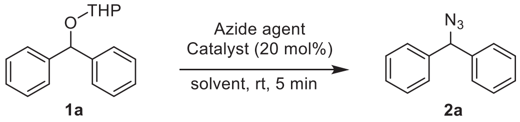
Result and discussion

First, various reagents were examined to react with 2-(benzhydryloxy)tetrahydro-2H-pyran (1a) in the presence of $TMSN_3$ to discover optimal catalysts. Employment of $MnCl_2$, $SnCl_2$,



Scheme 1. Direct transformations of protected benzyl alcohols.

Table 1. Screening of reaction conditions for the conversion of THP benzyl ether to azide[a].



Entry	Azide agent	Catalyst	Solvent	Yield[b] (%)
1	$TMSN_3$	$MnCl_2$	CH_2Cl_2	NR[c]
2	$TMSN_3$	$SnCl_2$	CH_2Cl_2	NR[c]
3	$TMSN_3$	$CuCl_2$	CH_2Cl_2	NR[c]
4	$TMSN_3$	$AlMe_3$	CH_2Cl_2	NR[c]
5	$TMSN_3$	$ZrCl_4$	CH_2Cl_2	NR[c]
6	$TMSN_3$	$ZnCl_2$	CH_2Cl_2	5
7	$TMSN_3$	$BiCl_3$	CH_2Cl_2	7
8	$TMSN_3$	$TiCl_4$	CH_2Cl_2	8
9	$TMSN_3$	$AlCl_3$	CH_2Cl_2	95
10	$TMSN_3$	CuI	CH_2Cl_2	NR[c]
11	NaN_3	$AlCl_3$	CH_2Cl_2	5
12	DPPA	$AlCl_3$	CH_2Cl_2	NR[c]
13	$TMSN_3$	$AlCl_3$	THF	NR[c]
14	$TMSN_3$	$AlCl_3$	1,4-dioxane	NR[c]
15	$TMSN_3$	$AlCl_3$	DMF	NR[c]
16	$TMSN_3$	$AlCl_3$	Toluene	51
17	$TMSN_3$	$AlCl_3$	MeCN	93
18	$TMSN_3$	$AlCl_3$	DCE	12
19	$TMSN_3$	No	CH_2Cl_2	NR[c]

[a] Reaction conditions: compound **1a** (1.0 mmol), azide agent (1.3 mmol), catalyst (0.2 mmol), room temperature, 5 min.
[b] Isolated yield after column purification. [c] No reaction.

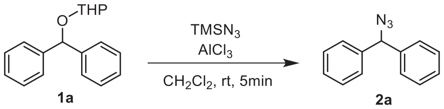
$CuCl_2$, $AlMe_3$, and $ZrCl_4$ as catalyst did not provide any desired product. Reactions using $ZnCl_2$, $BiCl_3$, and $TiCl_4$ did not provide the corresponding product in satisfactory yield: synthetic yields were less than 10% (Table 1, entries 6–8). Next, $AlCl_3$ was investigated as a catalyst for the reaction, and the target product was obtained in excellent yield (Table 1, entry 9). Utilization of CuI was also ineffective for generation of the corresponding product. NaN_3 and DPPA, the other azide agents, were also examined, but they proved to be less suitable for the direct reaction of benzyl THP ether to give the azido product. (Table 1, entries 11 and 12).

Solvent effect on the direct synthesis of azido product was investigated (Table 1, entries 13–18). Utilization of THF, 1,2-dioxane, and DMF as solvent did not generate the corresponding product, while toluene enhanced the synthetic yield of the target product (55% for toluene). When MeCN was used as solvent, the reaction readily generated the corresponding product in high yield (93%). Dichloroethane (DCE, $C_2H_4Cl_2$) was also tested; however, the reaction in DCE produced the target compound in low yield.

The efficiency of azide reagent ($TMSN_3$) and Lewis acid ($AlCl_3$) were investigated to find optimal amounts of $TMSN_3$ and $AlCl_3$ for the reaction. A series of reactions varying the amount of $TMSN_3$ with 2-(benzhydryloxy)tetrahydro-2H-pyran in the presence of a catalytic amount of $AlCl_3$ were performed. Employment of 3.0, 2.0, and 1.3 equiv. of $TMSN_3$ for the reaction provided the desired product in high yield, as shown in Table 2. Several different amounts of $AlCl_3$ were also tested to find a suitable amount for the reaction. Utilization of 1.0, 0.5, 0.3, and 0.2 equiv. of $AlCl_3$ in the reaction produced the target product in high yield (95%).

With optimized reaction conditions in hand, the scope of the direct conversion of various benzyl THP ethers to azido compounds using $AlCl_3$ was examined. First,

Table 2. Screening of amount of reagent and catalyst for the preparation of azide[a] .



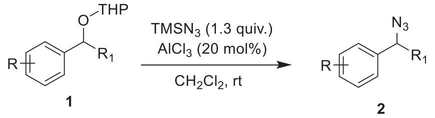
Entry	$TMSN_3$ (equiv)	$AlCl_3$ (equiv)	Time(min)	Yield[b] (%)
1	3	0.2	5	95
2	2	0.2	5	95
3	1.3	0.2	5	95
4	1	0.2	5	71
5	0.5	0.2	5	32
6	1.3	1.0	5	95
7	1.3	0.5	5	95
8	1.3	0.3	5	95
9	1.3	0.2	5	95
10	1.3	0.1	5	37
11	1.3	0.05	5	8
12	1.3	0.01	5	1

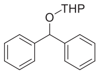
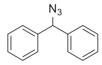
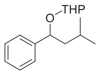
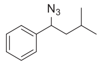
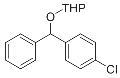
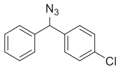
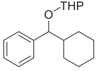
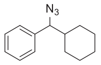
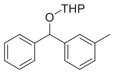
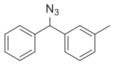
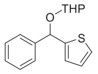
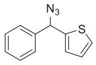
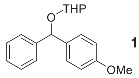
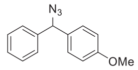
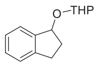
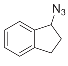
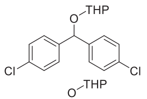
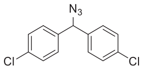
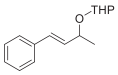
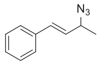
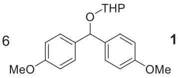
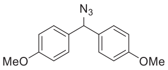
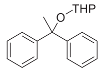
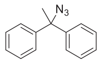
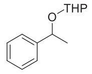
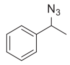
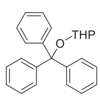
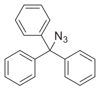
[a]Reaction conditions: compound **1a** (1.0 mmol), $TMSN_3$ (1.3 mmol), $AlCl_3$ (0.2 mmol), room temperature, 5 min. [b]Isolated yield after column purification.

mono-substituted benzhydrol THP ethers [2-(benzhydryloxy)tetrahydro-2H-pyrans)] were used to prepare azido products. 2-(Benzhydryloxy)tetrahydro-2H-pyrans bearing electron-donating groups (methyl, and methoxy) and an electron-withdrawing group (chloro) on the aromatic ring were treated with $TMSN_3$ in the presence of $AlCl_3$ to yield the corresponding azido products in high yields (Table 3, entries 1–4). Di-substituted benzhydrol THP ethers were also employed for the reaction with $TMSN_3$, and the target products such as 4,4′-(azidomethylene)bis(chlorobenzene) and 4,4′-(azidomethylene)bis(methoxybenzene) were successfully prepared in high yields (90% for 2e, and 95% for 2f). In addition, benzyl THP ethers containing various alkyl groups such as 1-phenylethan-1-ol THP ether containing a methyl group, 3-methyl-1-phenylbutan-1-ol THP ether containing an isobutyl group, and cyclohexyl(phenyl)methanol THP ether containing a cyclohexyl group were treated with $TMSN_3$ under the same reaction conditions to provide the corresponding azido products in the range of 88-93% (Table 3, entries 7–9). Reaction of phenyl(thiophen-2-yl)methanol THP ether containing a heterocyclic moiety was also tested, and 2-(azido(phenyl)methyl)thiophene was successfully synthesized (Table 3, entry10). Benzyl THP ethers derived from 1-indanol and 4-phenyl-3-buten-2-ol were also tested, affording the corresponding products in 93% and 90% yield, respectively (Table 3, entries 11 and 12). Reactions of tertiary benzyl THP ethers, which are more sterically hindered, were carried out, and they provided the corresponding azido products in high yields (Table 3, entries 13 and 14). Notably, the reaction of 2-(trityloxy)tetrahydro-2H-pyran (1n) readily provided the target azido product in 89% yield. These results suggest that the novel method using $TMSN_3$ and catalytic $AlCl_3$ could be effectively used to prepare azido compounds from a wide variety of benzyl THP ethers.

The allyl group is a widely utilized protecting group for alcohols in many multistep syntheses. However, to the best of our knowledge, there is no report of the direct synthesis of azido compounds from allyl benzyl ethers. Thus, this novel protocol using AlCl3 was applied to the direct conversion of allyl benzyl ethers to azido compounds, as shown in Table 4. Reactions of the mono-/di- substituted ((allyloxy)methylene)dibenzene bearing electron-withdrawing substituents (bromo, and fluoro) or

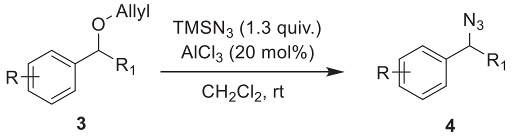
Table 3. Scope of synthesis of azides from various benzyl THP ethers[a].

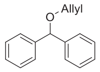
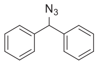
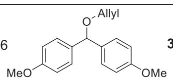
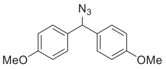
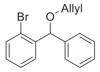
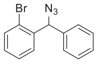
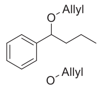
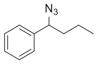
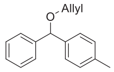
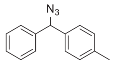
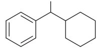
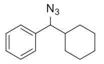
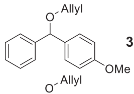
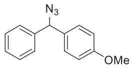
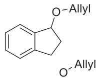
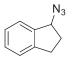
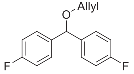
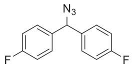
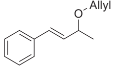
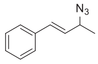
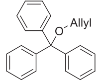
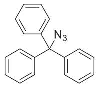


Entry	Benzyl THP ether	Product	Yield^b (%)	Entry	Benzyl THP ether	Product	Yield^b (%)
1	 **1a**	 **2a**	94	8	 **1h**	 **2h**	89
2	 **1b**	 **2b**	91	9	 **1i**	 **2i**	93
3	 **1c**	 **2c**	95	10	 **1j**	 **2j**	88
4	 **1d**	 **2d**	91	11	 **1k**	 **2k**	93
5	 **1e**	 **2e**	90	12	 **1l**	 **2l**	90
6	 **1f**	 **2f**	95	13	 **1m**	 **2m**	91
7	 **1g**	 **2g**	88	14	 **1n**	 **2n**	89

[a]Reaction conditions: compound **1** (1.0 mmol), TMSN$_3$ (1.3 mmol), AlCl$_3$ (0.2 mmol), room temperature, 5 min. [b]Isolated yield after purification by flash column chromatography.

Table 4. Scope of synthesis of azides from various allyl benzyl ethers[a].



Entry	Allyl benzyl ether	Product	Yield^b (%)	Entry	Allyl benzyl ether	Product	Yield^b (%)
1	 **3a**	 **4a**	94	6	 **3f**	 **4f**	95
2	 **3b**	 **4b**	91	7	 **3g**	 **4g**	90
3	 **3c**	 **4c**	93	8	 **3h**	 **4h**	92
4	 **3d**	 **4d**	92	9	 **3i**	 **4i**	92
5	 **3e**	 **4e**	93	10	 **3j**	 **4j**	94
				11	 **3k**	 **4k**	93

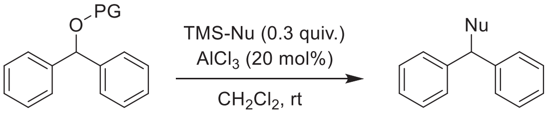
[a]Reaction conditions: compound **3** (1.0 mmol), TMSN$_3$ (1.3 mmol), AlCl$_3$ (0.2 mmol), room temperature, 5 min. [b]Isolated yield after column purification.

electron-donating substituents (methyl, and methoxy) with $TMSN_3$ successfully generated the target azido compounds in high yields (Table 4, entries 1–6).

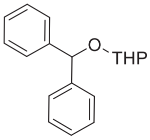
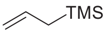
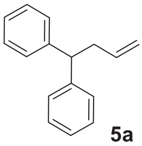
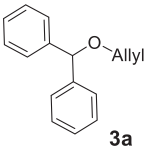
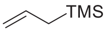
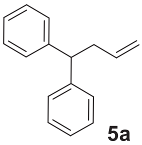
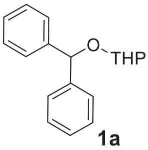
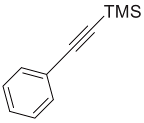
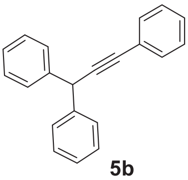
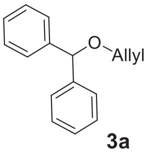
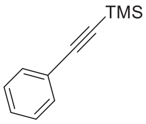
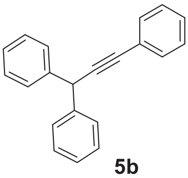
Allyl benzyl ethers containing an alkyl group such as propyl and cyclohexyl were treated with $TMSN_3$ to provide the corresponding products in high yield (Table 4, entries 7 and 8). Furthermore, reactions of allyl benzyl ethers derived from various types of alcohol including 1-indanol, 4-phenyl-3-buten-2-ol, and triphenylmethanol were conducted under the same reaction conditions, and the desired products were prepared in the range of 92% to 94% yield (Table 4, entries 9-11).

Next, the scope of this synthetic method was extended to direct nucleophilic substitution by carbon nucleophiles. As shown in Table 5, the benzyl THP ether or allyl benzyl ether was reacted with allyl-TMS or TMS-phenylacetylene in the presence of $AlCl_3$, and the target allylated and alkynylated products were successfully prepared in high yields. These results indicate that this $AlCl_3$ catalyzed protocol could be successfully used to form new C-C bonds directly from THP protected alcohols and allyl protected alcohols.

Table 5. Reaction of carbon nucleophiles with THP/allyl benzyl ethers[a].



1 or 3 **5**

Entry	Benzyl ethers	Nucleophile	Product	Yield[b] (%)
1	 **1a**		 **5a**	91
2	 **3a**		 **5a**	90
3	 **1a**		 **5b**	82
4	 **3a**		 **5b**	81

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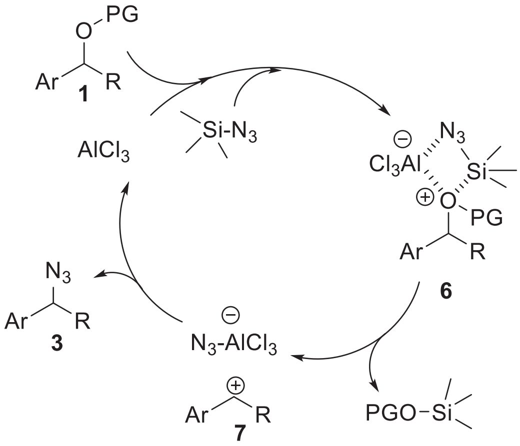
[a] Reaction conditions: compound **1** or **3** (1.0 mmol), $TMSN_3$ (1.3 mmol), $AlCl_3$ (0.2 mmol), room temperature, 30 min.
[b] Isolated yield after column purification.



Scheme 2. Proposed reaction pathway for generation of azido compounds from THP and allyl ethers.

A possible reaction pathway can be proposed, as shown in Scheme 2. The reaction begins with activation of the oxygen atom of the benzyl THP ether or allyl benzyl ether by $AlCl_3$ to give the secondary benzyl cation intermediate 7, and then attack by N_3 affords the corresponding azido product 3.

Conclusion

In conclusion, a novel facile method for the direct conversion of benzyl THP ethers and allyl benzyl ethers to azido compounds has been reported. In this study, $TMSN_3$ and $AlCl_3$ were used as the key azide reagent and catalyst for direct synthesis of azido compounds from benzyl THP ethers and allyl benzyl ethers. In addition, nucleophilic additions by carbon nucleophiles on benzyl THP ethers or allyl benzyl ethers were achieved *via* utilization of this catalytic protocol. Moreover, this method employed an inexpensive catalyst and was operationally simple. The method provides a novel approach to the direct transformation of benzyl THP ethers and allyl benzyl ethers.

Experimental

Reagents and solvents were commercially available and used as received. Column chromatography was performed using silica gel 60 (0.040–0.063 mm) and eluted with proper mixture (DCM/hexane). All of the new compounds were identified by 400 MHz ^1H and 100 MHz ^{13}C NMR spectra in deuterated chloroform ($CDCl_3$) with tetramethylsilane(TMS) as an internal reference, and high resolution mass spectroscopy. The identity of the known compounds was established by the comparison of their ^1H and ^{13}C NMR peaks with the authentic values.

General experimental procedure for the synthesis of azido compounds from THP protected alcohols (2a–2n)

To a mixture of THP-protected alcohol (**1a**) (0.269 g, 1.00 mmol) and $AlCl_3$ (0.027 g, 0.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise $TMSN_3$ (0.149 g, 1.3 mmol). The reaction mixture was stirred at room temperature for 5 min. After adding water (5 mL) to the mixture, the reaction mixture was extracted with EtOAc (2 × 5 mL), then the organic layer was dried over sodium sulfate and subsequently concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with 5% CH_2Cl_2 in hexane as eluent to afford the desired product **2a** (0.196 g, 94%).

General experimental procedure for the synthesis of azido compounds from allyl protected alcohols (4a–4k)

To a mixture of allyl-protected alcohol (**3a**) (0.224 g, 1.00 mmol) and $AlCl_3$ (0.027 g, 0.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise $TMSN_3$ (0.149 g, 1.3 mmol). The reaction mixture was stirred at room temperature for 5 min. After adding water (5 mL) to the mixture, the reaction mixture was extracted with EtOAc (2 × 5 mL), then the organic layer was dried over sodium sulfate and subsequently concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with 5% CH_2Cl_2 in hexane as eluent to afford the desired product **4a** (0.197 g, 94%).

General experimental procedure for the synthesis of carbon-carbon compounds from allyl/THP protected alcohols (5a–5b)

To a mixture of THP-protected alcohol (**1a**) (0.269 g, 1.00 mmol) and $AlCl_3$ (0.027 g, 0.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise TMS-Allyl (0.149 g, 1.3 mmol). The reaction mixture was stirred at room temperature for 30 min. After adding water (5 mL) to the mixture, the reaction mixture was extracted with EtOAc (2 × 5 mL), then the organic layer was dried over sodium sulfate and subsequently concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with 5% CH_2Cl_2 in hexane as eluent to afford the desired product **5a** (0.190 g, 91%).

Selected spectroscopic data

(Azidomethylene)dibenzene (2a): Light yellow oil (94%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 10H), 5.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.59 (2 C), 128.72 (4 C), 128.06 (2 C), 127.40 (4 C), 65.54; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{13}H_{12}N_3$ = 210.1031, found 210.1035.

(1-Azido-3-methylbutyl)benzene (2h): Light yellow oil (89%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 5H), 4.51 (dd, $J = 14.4$ Hz, $J = 14.4$ Hz,1H), 1.80 – 1.75 (m, 1H), 1.69 – 1.56 (m, 2H), 0.97 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.02, 128.78 (2 C), 128.19, 126.90 (2 C), 64.52, 45.06, 25.01, 22.63, 22.22; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{16}N_3$ = 190.1344, found 190.1347.

(Azidomethanetriyl)tribenzene (2n): Light yellow oil (89%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.14 (3 C), 128.48

(6 C), 128.20 (6 C), 127.70 (3 C), 77.15 (1 C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{19}H_{16}N_3$ = 286.1344, found 286.1348.

4,4′-(Azidomethylene)bis(fluorobenzene) (4e): Light yellow oil (93%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 4H), 7.10 – 7.05 (m, 4H), 5.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.67, 161.21, 135.26, 135.23, 129.09 (2 C), 129.01 (2 C), 115.82 (2 C), 115.61 (2 C), 67.12; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{13}H_{10}F_2N_3$ = 246.0843, found 246.0846.

Prop-2-yne-1,1,3-triyltribenzene (5b): Colorless oil (82%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.46 (m, 6H), 7.35 – 7.32 (m, 7H), 7.28 – 7.26 (m, 2H), 5.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.77 (2 C), 131.73 (2 C), 128.66 (4 C), 128.23 (2 C), 127.99 (1 C), 127.92 (4 C), 126.94 (2 C), 123.50 (1 C), 90.20 (1 C), 84.88 (1 C), 43.77 (1 C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{21}H_{17}$ = 269.1330, found 269.1332.

Disclosure statement

There are no conflicts to declare.

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