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Convenient and Direct Azidation of *sec*-Benzyl Alcohols by Trimethylsilyl Azide with Bismuth(III) Triflate Catalyst

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Abstract *sec*-Benzyl azides were efficiently prepared by bismuth(III)catalyzed direct azidation of *sec*-benzyl alcohols. The reaction was applied to a variety of substrates to provide the desired products in up to 99% yield within a short reaction time.

Key words azides, catalysis, bismuth, alcohols

Benzyl azide is a versatile reagent that can be used in several methods for the synthesis of nitrogen-containing compounds. For example, benzyl azide has been used as an important precursor to introduce an N-benzyl moiety into molecules in preparations of isoquinolines,¹ benzylamines,² and benzyltriazoles.³ Moreover, benzyl azide can be used in Schmidt reactions⁴ and Schmidt–Mannich-type reactions⁵ involving an azide rearrangement process. We have studied the use of benzyl azide in an azide rearrangement to generate N-aryliminium ions for use in the synthesis of nitrogencontaining compounds such as N-arylmethyl arenes,⁶ quinolines,⁷ or phenanthridines.⁸ Because of the important synthetic potential of benzyl azides, development of methods for their synthesis is still an active area of research. In general, benzyl azides can be synthesized by converting the hydroxy group of a benzyl alcohol into a better leaving group, with subsequent azidation by sodium azide,⁹ whereas direct azidation can also be performed by using sodium azide under thermal conditions.¹⁰ Because organic azides, especially low-molecular-weight azides, are sensitive to external factors such as heat, light, or pressure, which can cause them to explode when handled in large quantity, several milder synthetic methods have been established employing diphenyl azidophosphate,11 di-4-nitrophenyl azidophosphate,¹² or 2-azido-4,5-dihydro-1,3-dimethyl-1H-imidaz-



olium hexafluorophosphate¹³ as an azidation agent. However, some of these conditions are inefficient for the synthesis of secondary and tertiary arylmethyl azides because a competing elimination pathway leads to low yields of the desired products, especially in the case of electron-rich benzyl alcohols. Among the various methods available, the use of a combination of a Lewis acid and trimethylsilyl azide is one of the best methods for the conversion of alcohols directly into azides.¹⁴ However, combinations of several Lewis acids with trimethylsilyl azide are inefficient in direct azidation of *sec*-benzylic alcohols because of the formation of dimeric ether side products **4**, whereas protected benzyl alcohols can be successfully converted into azidation products by treatment with trimethylsilyl azide and iron(III) chloride or bromide, as shown in Scheme 1.¹⁵



In this work, we present a convenient method for the synthesis of *sec*-benzylic azides by direct azidation with trimethylsilyl azide and a catalytic amount of bismuth(III) triflate at room temperature (Scheme 2).

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Scheme 2 Bi(OTf)₃-catalyzed direct azidation of *sec*-benzyl alcohols for the preparation of *sec*-benzyl azides

Because metal triflates are well-established activators of benzyl alcohols to give carbocation,¹⁶ we decided to screen optimal conditions for the conversion of 1-phenylethanol (1a) into the corresponding azide 2a by using a combination of a metal triflate and trimethylsilyl azide. The ratio of the products was determined by ¹H NMR spectroscopy (Table 1). The reaction using 1 mol% of indium(III) triflate in dichloromethane gave the product **2a** in 52% yield at room temperature, together with the recovered starting material and the dimeric ether **4a** as a byproduct (Table 1, entry 1). Switching the solvent to acetonitrile gave none of the desired product (entry 2). When we conducted the reaction at 0 °C in dichloromethane, we obtained the azidation product 2a in only 9% vield (entry 3). When scandium(III) or ytterbium(III) triflate was used, we obtained only trace amount of the desired product 2a, and the silyl-protected compound **3a** was the major product in both cases (entries 4 and 5). The yield of azidation product 2a was improved to 69% when 1% of bismuth(III) triflate was used in the reaction (entry 6). On increasing the amount of bismuth(III) triflate to 2 mol%, the yield of the desired azide was slightly lowered (entry 7). The azidation product was also obtained in a lower yield when 1,2-dichloroethane was used as the solvent (entry 8). Bismuth(III) triflate was therefore selected as the optimal catalyst because of the very low loading and mild reaction conditions required, even though starting material 1a remained and the ether byproduct **4a** was also formed. Therefore, the use of 1 mol% bismuth(III) triflate and 1.2 equivalents of trimethylsilyl azide in dichloromethane was selected as the protocol of choice.

Having determined the optimal conditions, we investigated the scope and limitations of the method. 1-Phenylethanol (**1a**), when subjected to the optimal conditions, gave the desired product in 58% isolated yield (Table 2, entry 1); 1-(4-fluorophenyl)ethanol and 1-(4-chlorophenyl)ethanol also gave the corresponding azidation products in good yields (entries 2 and 3). With 1-(4-bromophenyl)ethanol (**1d**), the reaction required a longer time (6 h) and gave the desired product in 70% yield (entry 4). The reactions of 1-(4-methoxyphenyl)ethanol (**1e**) and 1-(3,4-dimethoxyphenyl)ethanol (**1f**) proceeded to completion within 5 min and gave the desired products in excellent yields (entries 5 and 6). This method was also found to be applicable to the bulkier substrate 1-(4-methoxyphenyl)pentan-1-ol (**1g**), which gave the corresponding prod-





| Entry | Conditions | Solvent | Product ratio 1/2a/3a/4a ª |
|-------|--|------------|--------------------------------------|
| 1 | In(OTf) ₃ (1 mol%), TMSN ₃ (1.2 equiv), r.t. | CH_2Cl_2 | 28:52:0:20 |
| 2 | In(OTf) ₃ (1 mol%), TMSN ₃ (1.2 equiv), r.t. | MeCN | no reaction |
| 3 | In(OTf) ₃ (1 mol%), TMSN ₃ (1.2 equiv), 0 °C | CH_2Cl_2 | 89:9:0:2 |
| 4 | Sc(OTf) ₃ (1 mol%), TMSN ₃ (1.2 equiv), r.t. | CH_2Cl_2 | _b |
| 5 | Yb(OTf) ₃ (1 mol%), TMSN ₃ (1.2 equiv), r.t. | CH_2Cl_2 | _ ^b |
| 6 | $Bi(OTf)_3$ (1 mol%), TMSN ₃ (1.2 equiv), r.t. | CH_2Cl_2 | 19: 69 :0:12 |
| 7 | $Bi(OTf)_3$ (2 mol%), TMSN ₃ (1.2 equiv), r.t. | CH_2Cl_2 | 19:67:0:14 |
| 8 | $Bi(OTf)_3$ (1 mol%), TMSN ₃ (1.2 equiv), r.t. | CH_2Cl_2 | 32:54:0:14 |
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^a By ¹H NMR spectroscopy. ^b The ratio of products could not be determined.

uct 2g in 98% yield (entry 7). Diphenylmethanol (1h) was smoothly converted into the corresponding product in 83% yield, and (4-methoxyphenyl)(phenyl)methanol (1i) gave the corresponding product 2i in excellent yield. These results showed that, in comparison with electronically neutral or electron-withdrawing groups, the presence of an electron-donating group on the substrate facilitates the azidation reaction. 1-(2-Naphthyl)ethanol, indan-1-ol, and 1,2,3,4-tetrahydronaphthalen-1-ol were all compatible with our conditions and gave the corresponding azidation products in good to excellent yields (entries 10-12). However, this method was not applicable to the azidation of ethyl 3-hydroxy-3-phenylpropanoate (1m), which gave the trimethylsilyl-protected product 3m in 34% yield, together with the unreacted starting material as the major component (entry 13). We also examined the azidation of the primary and tertiary benzyl alcohols **1n**-**p** (entries 14–16); azidation of benzyl alcohol (**1n**) failed to give benzyl azide (2n), whereas 4-methoxybenzyl alcohol (1o) gave only a trace of the corresponding azide **20**; the starting materials were recovered in both cases. These results suggested that primary benzyl alcohols do not generate the corresponding carbocation efficiently in the presence of bismuth(III) triflate as a catalyst. In case of the tertiary benzyl alcohol **1p**, the reaction proceeded uneventfully to give the desired product 2p with high efficiency. Similarly, 2-methyl-4phenylbut-3-yn-2-ol (1q) also underwent rapid conversion into the desired azide 2q in good yield (entry 17). Unfortunately, the sec-allylic benzyl alcohol 1r could not be successfully converted into the corresponding azide but gave a complex mixture instead.

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Synthesis J. Tummatorn et al. Table 2 Scope of Substrates

| | | R ¹ H - | Bi(OTf) ₃ (1 mol%) TMSN ₃ (1.2 equiv) CH ₂ Cl ₂ , r.t. | \rightarrow R^{1} N_{3} | | |
|-------|-----------|-----------------------|--|-------------------------------|------------|------------|
| Entry | Substrate | | Product | | Time (min) | Yieldª (%) |
| 1 | 1a | OH OH | 2a | N ₃ | 60 | 58 |
| 2 | 16 | PH PH | 2Ь | F N3 | 60 | 64 |
| 3 | 1c | OH CI | 2c | CI N3 | 60 | 60 |
| 4 | 1d | OH Br | 2d | Br N ₃ | 360 | 70 |
| 5 | 1e | OH MeO | 2e | MeO N3 | 5 | 98 |
| 6 | 1f | MeO MeO | 2f | MeO MeO | 5 | 98 |
| 7 | 1g | OH Bu MeO | 2g | N ₃ Bu | 5 | 98 |
| 8 | 1h | OH | 2h | N ₃ | 20 | 83 |
| 9 | 1i | OH Ph MeO | 2i | N ₃ MeO | 5 | 98 |
| 10 | 1j | ОН | 2j | N ₃ | 60 | 80 |

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| Entry | Substrate | | Product | | Time (min) | Yieldª (%) |
|-------|-----------|--|---------|--------------------------|------------|-------------------|
| 11 | 1k | ОН | 2k | N ₃ | 10 | 99 |
| 12 | 11 | OH | 21 | N ₃ | 10 | 83 |
| 13 | 1m | OH O OEt | 3m | TMSO O OEt | 180 | 34 |
| 14 | 1n | ОН | 2n | N ₃ | 180 | n.r. ^b |
| 15 | 10 | МеО | 20 | MeO N ₃ | 180 | trace |
| 16 | 1p | OH | 2р | N ₃ | 180 | 90 |
| 17 | 1q | → → → → → → → → → → → → → → → → → → → | 2q | $\underbrace{\ }_{N_3}$ | 30 | 87 |
| 18 | 1r | OH Ph MeO | 2r | N ₃ MeO Ph | 30 | - |

^a Isolated yield.

^b No reaction.

To demonstrate the utility of our method in scalable syntheses, the reactions of alcohols **1f** and **1k** were conducted on a gram scale to give the corresponding azides **2f** and **2k** in excellent yields (Scheme 3).



In conclusion, we have developed a convenient method for the direct azidation of unprotected *sec*-benzyl alcohols using only a 1 mol% loading of bismuth(III) triflate as a catalyst. This method can be applied to a wide scope of substrates, providing the desired products in good to excellent yields and within short reaction times. The scalability and convenience of this protocol make it a highly practical procedure for the preparation of *sec*-benzyl azides.

All reagents and solvents were of commercial grade and were used as received from the suppliers. ¹H and ¹³C NMR spectra were recorded in CDCl₃ with a Bruker Avance 300 MHz NMR spectrometer; chemical shifts are reported in ppm relative to TMS. IR spectra were recorded using a PerkinElmer Spectrum One FT-IR spectrophotometer. High-resolution mass spectra (HRMS) and electron-impact mass spectra (EI-MS) were recorded on a Bruker Daltonics microTOF mass spectrometer.

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sec-Benzyl Azides 2: General Procedure

 $Bi(OTf)_3$ (1.0 mol%) was added to a solution of the appropriate secbenzyl alcohol (1.0 equiv) and TMSN_3 (1.2 equiv) in CH_2Cl_2 (4.0 mL/mmol) at r.t. When the reaction was complete (TLC), the solvent was removed and the crude material was purified by column chromatography.

(1-Azidoethyl)benzene (2a)

The crude product was purified on silica gel (eluent: hexane–EtOAc, 100:0 to 95:5) to give the product as a colorless oil; yield: 234.8 mg (58%).

IR (neat): 2926, 2111, 700 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.38–7.27 (m, 5 H), 4.48 (q, *J* = 6.9 Hz, 1 H), 1.51 (d, *J* = 6.9 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 140.8, 128.7, 128.0, 126.3, 61.0, 21.5.

1-(1-Azidoethyl)-4-fluorobenzene (2b)

The crude product was purified on silica gel (eluent: hexane–EtOAc, 100:0 to 95:5) to give the product as a colorless oil; yield: 164.8 mg (64%).

IR (neat): 2101, 1604, 1509, 1223 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.33–7.25 (m, 2 H), 7.10–7.02 (m, 2 H), 4.60 (q, J = 6.9 Hz, 1 H), 1.51 (d, J = 6.9 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 162.4 (d, J_{CF} = 245 Hz), 136.7, 128.1 (d, J_{CF} = 8 Hz), 115.6 (d, J_{CF} = 21 Hz), 60.3, 21.6.

TOF-HRMS: m/z [M + H – N₂]⁺ calcd for C₈H₉FN: 138.0708; found: 138.0713.

1-(1-Azidoethyl)-4-chlorobenzene (2c)

The crude product was purified on silica gel (eluent: hexane-EtOAc, 100:0 to 95:5) to give the product as a colorless oil; yield: 169.6 mg (60%).

IR (neat): 2092, 1493, 1242, 1092 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.39–7.35 (m, 2 H), 7.30–7.27 (m, 2 H), 4.62 (q, *J* = 6.9 Hz, 1 H), 1.53 (d, *J* = 6.9 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 139.4, 133.8, 128.9, 127.7, 60.3, 21.5. EI-MS: m/z (%) = 181 (10) [M⁺], 129 (59), 111 (42), 73 (100).

1-(1-Azidoethyl)-4-bromobenzene (2d)

The crude product was purified on silica gel (eluent: hexane–EtOAc, 100:0 to 95:5) to give the product as a colorless oil; yield: 533.0 mg (70%).

IR (neat): 2101, 1489, 1244, 823 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.49 (dd, *J* =8.7, 1.8 Hz, 2 H), 7.18 (dd, *J* = 10.8, 2.4 Hz, 2 H), 4.58 (q, *J* = 6.6 Hz, 1 H), 1.50 (d, *J* = 6.9 Hz, 3 H). ¹³C NMR (75 MHz, CDCl₃): δ = 139.9, 131.9, 128.0, 122.0, 60.4, 21.5. EI-MS: *m/z* (%) = 226 (5) [M⁺], 129 (60), 98 (62), 73 (100).

1-(1-Azidoethyl)-4-methoxybenzene (2e)

The crude product was purified on silica gel (eluent: hexane-EtOAc, 95:5) to give the product as a colorless oil; yield: 345.3 mg (98%). IR (neat): 2094, 1610, 1510, 1245 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.28–7.23 (m, 2 H), 6.93–6.88 (m, 2 H), 4.56 (q, J = 6.6 Hz, 1 H), 3.80 (s, 3 H), 1.50 (d, J = 6.9 Hz, 3 H).

 ^{13}C NMR (75 MHz, CDCl₃): δ = 159.4, 132.8, 127.6, 114.0, 60.6, 55.2, 21.4.

EI-MS: *m*/*z* (%) = 177 (14) [M⁺], 149 (60), 111 (61).

4-(1-Azidoethyl)-1,2-dimethoxybenzene (2f)

The crude product was purified on silica gel (eluent: hexane–EtOAc, 90:10) to give the product as a colorless oil; yield: 115.4 mg (98%), 2.38 g (99%, gram-scale synthesis).

IR (neat): 2096, 1515, 1235, 1025 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 6.85–6.83 (m, 3 H), 4.56 (q, *J* = 6.9 Hz, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 1.51 (d, *J* = 6.9 Hz, 3 H).

 ^{13}C NMR (75 MHz, CDCl₃): δ = 149.0, 148.7, 133.2, 118.6, 110.9, 109.3, 60.8, 55.7, 21.4.

TOF-HRMS: m/z [M + Na]⁺ calcd for C₁₀H₁₃N₃NaO₂: 230.0900; found: 230.0911.

1-(1-Azidopentyl)-4-methoxybenzene (2g)

The crude product was purified on silica gel (eluent: hexane-EtOAc, 95:5) to give the product as a colorless oil; yield: 324.4 mg (98%).

IR (neat): 2091, 1611, 1513, 1247 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.22 (d, *J* = 8.7 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 4.34 (t, *J* = 7.2 Hz, 1 H), 3.80 (s, 3 H), 1.89–1.59 (m, 2 H), 1.40–1.24 (m, 4 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

 ^{13}C NMR (75 MHz, CDCl₃): δ = 159.4, 131.9, 128.1, 114.0, 65.9, 55.2, 35.7, 28.4, 22.3, 13.9.

EI-MS: *m*/*z* (%) = 219 (0.5) [M⁺], 127 (40), 104 (92), 97 (60), 73 (100).

1,1'-(Azidomethylene)dibenzene (2h)

The crude product was purified on silica gel (eluent: hexane–EtOAc, 95:5) to give the product as a colorless oil; yield: 311.3 mg (83%).

IR (neat): 2094, 1237, 695 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.38–7.26 (m, 10 H), 5.70 (s, 1 H). ¹³C NMR (75 MHz, CDCl₃): δ = 139.6, 128.7, 128.0, 127.4, 68.5.

EI-MS: *m*/*z* (%) = 209 (3) [M⁺], 167 (100), 152 (15), 77 (21).

1-[Azido(phenyl)methyl]-4-methoxybenzene (2i)

The crude product was purified on silica gel (eluent: hexane-EtOAc, 90:10) to give the product as a colorless oil; yield: 777.3 mg (98%).

IR (neat): 2094, 1610, 1510, 1245, 1031 cm⁻¹.

 ^1H NMR (300 MHz, CDCl_3): δ = 7.37–7.25 (m, 5 H), 7.24–7.19 (m, 2 H), 6.90–6.86 (m, 2 H), 5.67 (s, 1 H), 3.78 (s, 3 H).

 ^{13}C NMR (75 MHz, CDCl_3): δ = 159.4, 139.9, 131.7, 128.8, 128.7, 127.9, 127.3, 114.1, 68.1, 55.3.

EI-MS: *m*/*z* (%) = 239 (4) [M⁺], 197 (100), 167 (11).

2-(1-Azidoethyl)naphthalene (2j)

The crude product was purified on silica gel (eluent: hexane–EtOAc, 100:0 to 95:5) to give the product as a colorless oil; yield: 438.5 mg (80%).

IR (neat): 2098, 1242, 747 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.88–7.76 (m, 4 H), 7.53–7.43 (m, 3 H), 4.78 (q, *J* = 6.6 Hz, 1 H), 1.61 (d, *J* = 6.9 Hz, 3 H).

 ^{13}C NMR (75 MHz, CDCl₃): δ = 138.2, 133.2, 133.1, 128.7, 128.0, 127.7, 126.4, 126.2, 125.3, 124.2, 61.3, 21.6.

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EI-MS: *m*/*z* (%) = 197 (7) [M⁺], 149 (60), 111 (28).

1-Azidoindane (2k)

The crude product was purified on silica gel (eluent: hexane–EtOAc, 90:10) to give the product as a colorless oil; yield: 129.7 mg (99%), 2.53 g (97%, gram-scale synthesis).

IR (neat): 2922, 2093, 749 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.39 (d, *J* = 6.6 Hz), 1 H, 7.31–7.21 (m, 3 H), 4.85 (q, *J* = 4.8 Hz, 1 H), 3.12–3.02 (m, 1 H), 2.91–2.81 (m, 1 H), 2.49–2.37 (m, 1 H), 2.16–2.06 (m, 1 H).

 ^{13}C NMR (75 MHz, CDCl₃): δ = 143.6, 140.6, 128.8, 126.8, 125.0, 124.5, 65.8, 32.5, 30.4.

EI-MS: *m*/*z* (%) = 159 (5) [M⁺], 149 (90), 112 (39), 57 (100).

1-Azido-1,2,3,4-tetrahydronaphthalene (21)

The crude product was purified on silica gel (eluent: hexane–EtOAc, 90:10) to give the product as a colorless oil; yield: 470.2 mg (83%).

IR (neat): 2090, 1232, 740 cm⁻¹.

 ^1H NMR (300 MHz, CDCl_3): δ = 7.31–7.12 (m, 4 H), 4.56 (t, J = 3.9 Hz, 1 H), 2.89–2.69 (m, 2 H), 2.06–1.90 (m, 3 H), 1.87–1.77 (m, 1 H).

¹³C NMR (75 MHz, CDCl₃): δ = 137.3, 133.7, 129.4, 129.1, 128.1, 126.1, 59.5, 29.1, 28.7, 18.9.

EI-MS: *m*/*z* (%) = 173 (14) [M⁺], 167 (44), 149 (80), 57 (100).

Ethyl 3-Phenyl-3-(trimethylsiloxy)propanoate (2m)

The crude product was purified on silica gel (eluent: hexane-EtOAc, 100:0 to 95:5) to give the product as a colorless oil; yield: 46.0 mg (34%).

IR (neat): 1737, 1250, 1049, 839 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.35–7.19 (m, 5 H), 5.14 (dd, J = 9.3, 4.2 Hz, 1 H), 4.20–4.04 (m, 2 H), 2.70 (dd, J = 14.7, 9.0 Hz, 1 H), 2.55 (dd, J = 14.7, 4.2 Hz, 1 H), 1.23 (td, J = 7.2, 1.2 Hz, 3 H), 0.00 (s, 9 H).

 ^{13}C NMR (75 MHz, CDCl_3): δ = 171.2, 143.9, 128.3, 127.5, 125.8, 72.0, 60.5, 46.2, 14.3, 14.2.

EI-MS: *m*/*z* (%) = 266 (5) [M⁺], 178 (99), 149 (58), 97 (77), 57 (100).

(1-Azido-1-methylethyl)benzene (2p)

The crude product was purified on silica gel (eluent: hexane–EtOAc, 100:0 to 90:10) to give the product as a colorless oil; yield: 334.1 mg (90%).

IR (neat): 2100, 1462, 1260 cm⁻¹.

 ^1H NMR (300 MHz, CDCl_3): δ = 7.46–7.42 (m, 2 H), 7.38–7.33 (m, 2 H), 7.30–7.23 (m, 1 H), 1.63 (s, 6 H).

¹³C NMR (75 MHz, CDCl₃): δ = 144.6, 128.5, 127.4, 125.1, 63.8, 28.3. EI-MS: *m/z* (%) = 161 (15) [M⁺], 149 (57), 97 (32), 57 (100).

(3-Azido-3-methylbut-1-yn-1-yl)benzene (2q)

The crude product was purified on silica gel (eluent: hexane-EtOAc, 100:0 to 95:5) to give the product as a colorless oil; yield: 442.4 mg (87%).

IR (neat): 2096, 1159, 698 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.47–7.44 (m, 2 H), 7.32–7.30 (m, 3 H), 1.58 (s, 6 H).

 ^{13}C NMR (75 MHz, CDCl₃): δ = 131.8, 128.6, 128.3, 122.1, 88.9, 84.7, 56.8, 29.1.

TOF-HRMS: m/z [M + H]⁺ calcd for C₁₁H₁₂N₃: 186.1026; found: 186.1027.

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