Cobalt-Catalyzed Synthesis of Tertiary Azides from \( \alpha,\alpha \)-Disubstituted Olefins under Mild Conditions Using Commercially Available Reagents

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Received 12 September 2007

Abstract: The use of commercially available azide sources is presented for the cobalt-catalyzed hydroazidation reaction. \( \alpha,\alpha \)-Disubstituted olefins with a variety of functional groups were employed as substrates, providing tertiary azides in useful yields.

Key words: alkenes, hydroazidation, homogeneous catalysis, cobalt, silanes

The use of organic azides as nucleophiles, electrophiles or nitrene precursors demonstrates their unique position in organic chemistry.1 Their synthetic utility is represented by their easy conversion to amines2 and by cycloaddition reactions.3 Recently, they attracted much attention especially in biochemistry for the Staudinger ligation4 and click chemistry.5 Primary and secondary alkyl azides are commonly prepared by classic nucleophilic substitution, but tertiary azides are more difficult to access by this approach.1 Moreover, substrates with a suitable leaving group are usually not readily available and have to be prepared. The hydroazidation of olefins represents a more direct access to these interesting compounds. Such an approach, however, is limited to alkenes that give rise to stabilized carbocations and requires excess hydrazoic acid (HN\(_3\))6 or trimethylsilyl azide (TMSN\(_3\))7 or zeolite-supported sodium azide (NaN\(_3\)).8 Conjugate additions to unsaturated carbonyl compounds9 and several multifunctionalization methods have been developed as well.10 Given the limitations of the known processes, a new azidation protocol was deemed desirable.

We have recently described a cobalt-catalyzed hydroazidation reaction of unactivated olefins 1 using tosyl azide (TsN\(_3\)) and a silane.11 We discovered that the diphenylglycine-derived ligand 2 provided the highest reactivity in the hydroazidation reaction. Excellent Markovnikov selectivity was observed and, importantly, tertiary azides were accessible by this method when geminally disubstituted and trisubstituted olefins were employed. In this paper, we describe the azidation of olefins under milder conditions with commercially available reagents, which are marketed as safe alternatives to TsN\(_3\) (Scheme 1).

In our ongoing investigations we have conducted a detailed study into the effect of catalyst, silane and tert-butyl hydroperoxide (t-BuOOH) additives, including mechanistic investigations.12 Furthermore, we observed that the structure of the azide source had a significant influence on the reaction. The arylsulfonyl azide scaffold proved to be the best and three compounds were recognized as efficient hydroazidating agents. All of them however, had to be prepared in advance and, therefore, we decided to test the more readily available arylsulfonyl azides. Such an azide source would render the method even more practical as all the components, including ligand 2, would be commercially available.

Using our standard conditions13 and 4-phenylbutene (1a) as a test substrate, we examined four different commercially available azide sources 4–7 (Scheme 2).14 4-Acetamidobenzenesulfonyl azide (4) was the best reagent, giving azide 3a in 82% yield after 1.5 hours. 4-Carboxybenzenesulfonyl azide (5) and benzenesulfonyl azide functionalized silica (7) were less active, providing the hydroazidation product 3a in 48% and 59% yield, respectively. Polymer-bound benzenesulfonyl azide (6) failed to give any product at all. With sulfonyl azide 4, we could improve the yield of 3a to 92% by conducting the reaction at 0 °C. Nonetheless, when submitting the sterically more challenging disubstituted olefin 1b, we were not able to get high conversions to the product 3b, even after varying the reaction conditions. It was apparent that sulfonyl azide...
could be easily modified given the carboxylic functionality. Deprotonation with sodium ethoxide provided the corresponding sodium salt \(8\) as a bench-stable, amorphous solid. To our delight, 1.5 equivalents of \(8\) with 6 mol% of catalyst, 30 mol% of \(\text{t-BuOOH}\) and two equivalents of tetramethyldisiloxane (TMDSO), was able to completely convert the disubstituted olefin \(1b\) into the corresponding azide \(3b\) in 92% yield (Scheme 3).

It is important to note that the reaction was heterogeneous since \(8\) was poorly soluble in ethanol. Next, we optimized the synthesis in order to obtain \(8\) in reasonable purity. Using sodium hydride in tetrahydrofuran at room temperature, we could obtain sodium 4-azidosulfonylbenzoate (8) in 86% yield and 95% purity (confirmed by \(^1\)H NMR). With a reliable procedure in hand, we proceeded to examine the scope of the hydroazidation reaction (Table 1).

### Table 1  Hydroazidation of Geminally Disubstituted Olefins with \(8^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1c)</td>
<td>(3c)</td>
<td>7</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>(1b)</td>
<td>(3b)</td>
<td>4</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>(1d)</td>
<td>(3d)</td>
<td>7</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>(1e)</td>
<td>(3e)</td>
<td>7</td>
<td>48</td>
</tr>
</tbody>
</table>

\(^{a}\) Reagents and conditions: Co(BF\(_4\))\(_2\)-6H\(_2\)O (6 mol%), ligand 2 (6 mol%), alkene (0.5 mmol), azide 8 (0.75 mmol), \(\text{t-BuOOH}\) (28 mol%), TMDSO (1 mmol), EtOH (2.5 mL), argon, 23 °C.
In our investigations we found that geminally disubstituted olefins were especially good substrates for the reaction, and as these compounds provide tertiary azides, which are difficult to prepare by other methods, we decided to focus on this class of alkene.

All olefins showed excellent Markovnikov selectivity as linear azides were never observed. A simple alkene and a protected alcohol were good substrates for the reaction (entries 1 and 2). In contrast to the protocol using tosyl azide (TsN₃), free alcohols could be employed, providing the corresponding azides in good yields (entries 3 and 11). Ester (entries 4–6) amides were well tolerated (entry 7) and substrates with an alkene functionality connected to either the O-end of an amino acid through an ester linkage (entries 8, 9 and 11) or to the N-end through an amide bond (entry 10), give interesting products in useful yields. Alkenes conjugated to stabilizing groups such as an ester or a phenyl showed no conversion at all and thus represent a limitation of the process.

Although sodium 4-azidosulfonylbenzoate (8) is an easy to handle, stable solid, we were interested in forming the reagent in situ, thus avoiding the pre-formation and isolation process. Formation of the sodium salt of carboxybenzenesulfonyl azide 5 in situ resulted in a very dense heterogeneous mixture and the stirring was not efficient. Interestingly, when using the pre-formed sodium salt 8, the mixture was less dense and stirring was never problematic. Finally, mixing azide 5 with triethylamine in ethanol formed the triethylammonium salt as a clear homogeneous mixture. Simple addition of Co(BF₄)₂·6H₂O (6 mol%), ligand 2 (6 mol%), t-BuOOH (30 mol%), TMDSO (2 equiv) and alkene 1b (1 equiv) to this clear solution (1.5 equiv of azide 5 and 1.43 equiv Et₃N), resulted in a smooth reaction providing tertiary azide 3b in 93% yield (Scheme 4).

In order to compare the two reagents [sodium 4-azidosulfonylbenzoate (8) versus triethylammonium 4-azidosulfonyl benzoate], several alkenes were submitted to the hydroazidation reaction with the in situ formed triethylammonium azidosulfonyl benzoate (Table 2).

Alkenes 1b and 1c gave practically the same yields as with the pre-formed azide 8 (Table 2, entries 1 and 2). Esters gave comparable results as well, with 1e being slightly more active (Table 2, entries 3 and 4). However, substrates where the alkene functionality was connected to an amino acid through an ester bond provided the corresponding azide in lower yields (Table 2, entries 5 and 6). These results indicate that the two protocols are complementary, with the pre-formed azide 8 being slightly more active and the in situ protocol being more straightforward. An advantage of both protocols is the easy removal of any excess reagent in the aqueous work-up.

### Table 2  Hydroazidation of Geminally Disubstituted Olefins with Triethylammonium 4-Azidosulfonylbenzoate Formed in situ

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1c</td>
<td>3c</td>
<td>7</td>
<td>99</td>
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<tr>
<td>3</td>
<td>Ph</td>
<td>3e</td>
<td>66 18</td>
<td>76</td>
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<td>3f</td>
<td>11 6</td>
<td>62</td>
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<tr>
<td>6</td>
<td>Boc</td>
<td>3j</td>
<td>6</td>
<td>79</td>
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</table>

*Reagents and conditions: azide 5 (0.75 mmol), Et₃N (0.715 mmol), Co(BF₄)₂·6H₂O (6 mol%), ligand 2 (6 mol%), t-BuOOH (30 mol%), TMDSO (2 equiv) and alkene 1b (1 equiv) to this clear solution (1.5 equiv of azide 5 and 1.43 equiv Et₃N), resulted in a smooth reaction providing tertiary azide 3b in 93% yield (Scheme 4)."
possibilities for drug discovery in the context of click chemistry and permits their use in bioconjugation via Staudinger ligation. Studies in order to better understand the similarities and differences between the processes, employing various azide sources, are being conducted.

All reactions were carried out under an atmosphere of argon or nitrogen. All chemicals were purchased from commercial suppliers and used as such unless stated otherwise. Compounds 1b, 1c, 2, 3a, 3b, 3c, 3d, and 3e were synthesized according to literature procedures. Flash chromatography was performed using Brunschwig silica 32–63, 60 Å. TLC was performed on Merck silica gel 60 F254, TLC glass plates and visualized with UV light and peramannic acid stain. Melting points were measured on a Büchi 510 melting point apparatus using open glass capillaries; the data are uncorrected. Optical rotation measurements were carried out on a Jasco DIP-1000 polarimeter. 1H NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer in CDCl3 or DMSO-d6, all signals are reported in ppm with the internal CHCl3 signal at 7.26 ppm or the internal DMSO signal at 2.50 ppm as standard.

CAUTION: Azides are potentially hazardous compounds and adequate safety measures should be taken. Reactions, especially when involving larger quantities or heating, should be conducted behind safety shields.

3-Methyl-N-phenylbut-3-eneamide (1h)
3-Methylbut-3-enioic acid (250 mg, 2.50 mmol, 1.00 equiv) was dissolved in CH2Cl2 (3 mL) at r.t. under argon. DMAP (8 mg, 0.063 mmol, 0.025 equiv) and aniline (458 µL, 5.00 mmol, 2.00 equiv) were added, the mixture was cooled to 0–5 °C (ice bath) and DCC (516 mg, 2.50 mmol, 1.00 equiv) was added. The mixture was stirred for 15 min at this temperature and then at r.t. for 4 h. CH2Cl2 (8 mL) was added, the precipitate was filtered off and the resulting homogeneous solution was washed with HCl (10%, 10 mL) and sat. NaHCO3 (10 mL). The solvent was evaporated and the crude product was purified by flash chromatography (hexane–EtOAc, 1:1) to give 1h.

Yield: 348 mg (79%); colorless solid; Rf = 0.5 (hexane–EtOAc, 7:3); [α]D20 −10.9 (c 1, CHCl3).

IR: 3371 (m), 3078 (w), 2978 (s), 2936 (m), 2865 (m), 1720 (s), 1650 (w), 1540 (m), 1435 (m), 1355 (m), 1234 (s), 1004 (m), 891 (m), 692 (s) cm–1.

1H NMR (CDCl3, 300 MHz): δ = 7.52–7.49 (m, 2 H, ArH), 7.47 (br s, 1 H, NH), 7.35–7.29 (m, 2 H, ArH), 7.13–7.08 (m, 1 H, ArH), 5.08 (m, 1 H, C=C), 5.02 (br s, 1 H, C=CH), 3.14 (s, 2 H, CH3), 1.87 (s, 3 H, CH3).

13C NMR (CDCl3, 75 MHz): δ = 168.55, 140.24, 137.72, 128.89, 115.72, 115.99, 47.30, 22.40.

HRMS (ESI): m/z calcd for C15H19NO3: 261.1360; found: 261.1359.

13C NMR (CDCl3, 75 MHz): δ = 171.96, 169.72, 159.42, 139.94, 135.90, 129.18, 128.26, 127.09, 115.51, 52.99, 52.13, 46.03, 37.94, 22.35, 18.74.

MS (ESI): m/z = 280.1 [M + Na]+.


(5)-Methyl-2-(3-Methylbut-3-enamido)-3-phenylpropanoate (1k)
Et2N (352 µL, 2.50 mmol, 1.00 equiv) was added to L-phenylalanine hydrochloride (539 mg, 2.50 mmol, 1.00 equiv) in CHCl3 (3 mL) at r.t. under argon, followed by 3-methylbut-3-enic acid (250 mg, 2.50 mmol, 1.00 equiv). The solution was cooled to 0–5 °C (ice bath) and DCC (516 mg, 2.50 mmol, 1.00 equiv) was added followed by a second portion of CHCl3 (1 mL). The reaction mixture was stirred at this temperature for 1 h and then at r.t. for 24 h. The precipitate formed was filtered off and washed with CHCI3 (10 mL). The organic phase was washed with HCl (10%, 5 mL) and sat. aq NaHCO3 (8 mL), the solvent was evaporated and the crude product was purified by two flash chromatographic separations (hexane–EtOAc, 1:1) to give 1k.

Yield: 302 mg (46%); colorless solid; Rf = 0.52 (hexane–EtOAc, 1:1); mp 59–61 °C; [α]D20 +48.6 (c 1, CHCl3).

IR: 3280 (m), 3070 (w), 2958 (w), 2346 (w), 1737 (m), 1646 (m), 1540 (m), 1435 (m), 1355 (m), 1234 (s), 1004 (m), 891 (m), 692 (s) cm–1.

1H NMR (CDCl3, 300 MHz): δ = 7.31–7.21 (m, 3 H, ArH), 7.10–7.07 (m, 2 H, ArH), 6.12 (d, J = 7.2 Hz, 1 H, NH), 4.84–4.84 (m, 3 H, C=CH2 and NCH), 3.73 (s, 3 H, OCH3), 3.16 (dd, J = 14.1 Hz, J = 6.0 Hz, 1 H, PhCH), 3.06 (dd, J = 14.1 Hz, J = 6.3 Hz, 1 H, PhCH2), 2.94 (s, 2 H, CH2), 1.70 (s, 3 H, CH3).

13C NMR (CDCl3, 75 MHz): δ = 171.96, 169.72, 159.42, 139.94, 135.90, 129.18, 128.26, 127.09, 115.32, 52.99, 52.13, 46.03, 37.94, 22.32.

HRMS (ESI): m/z calcd for C16H16NO3: 261.1360; found: 261.1359.

(5)-2-Methylallyl 2-(tert-Butyloxycarbonylamino)-3-hydroxypropanoate (1l)
Et2N (556 µL, 4.00 mmol, 1.00 equiv) was added to N-Boc-L-serine (821 mg, 4.00 mmol, 1.00 equiv) in CHCl3 (8 mL) at r t. under argon followed by 3-bromo-2-methylprop-1-ene (403 µL, 4.00 mmol, 1.00 equiv). The reaction mixture was stirred at r.t. for 24 h then CHCl3 (10 mL) was added and the mixture was washed with HCl (10%, 10 mL) and brine (15 mL). The solvent was evaporated and the crude product was purified by flash chromatography (hexane–EtOAc, 1:1) to give 1l.

Yield: 526 mg (51%); colorless oil; Rf = 0.54 (hexane–EtOAc, 1:1); [α]D20 −1.5 (c 1, CHCl3).
IR: 3435 (m), 2979 (m), 2936 (m), 1716 (s), 1506 (s), 1456 (m), 1393 (m), 1368 (s), 1345 (m), 1251 (m), 1164 (s), 1062 (m), 953 (w), 907 (w), 875 (w), 780 (w) cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 5.47 (br s, 1 H), 5.00 (s, 1 H, C=CH₂), 4.95 (s, 1 H, C=CH₂), 4.62 (d, J = 13.2 Hz, 1 H, CO₂CH₃), 4.56 (d, J = 13.2 Hz, 1 H, CO₂CH₃), 4.41 (br s, 1 H, 4.03–3.88 (m, 2 H, OCH₂), 2.45 (t, J = 6.3 Hz, 1 H, NCH₂), 1.76 (s, 3 H, CH₃), 1.45 [s, 9 H, C(CH₃)₃].

¹³C NMR (CDCl₃, 75 MHz): δ = 170.49, 155.73, 139.17, 113.57, 80.31, 68.81, 63.60, 55.77, 28.25, 19.38.

MS (ESI): m/z = 282.1 [M + Na].

Calcld for C₁₅H₂₃NO₃: C, 55.48; H, 8.16; N, 5.40. Found: C, 55.41; H, 8.19; N, 5.43.

Yield: 384 mg (86%; purity of 95% by ¹H NMR); colorless amor-phous solid; IR: 3619 (w), 3369 (w), 2352 (w), 2127 (s), 1605 (s), 1558 (m), 1393 (s), 1302 (m), 1166 (s), 1084 (m), 1016 (w), 845 (w), 743 (s), 688 (w), 606 (s) cm⁻¹.

Hydroazidation Reaction; Typical Procedure A

Co(BF₄)₂·6H₂O (10 mg, 0.03 mmol, 0.06 equiv) and ligand 2 (14 mg, 0.03 mmol, 0.06 equiv) were dissolved in EtOH (1 mL) at r.t. under argon. After 10 min, 3-methylbut-3-enylbenzene (73 mg, 0.75 mmol, 1.00 equiv) was added and the mixture was stirred until the mixture became a clear colorless solution (15–20 min). Co(BF₄)₂·6H₂O (10 mg, 0.03 mmol, 0.06 equiv) and ligand 2 (14 mg, 0.03 mmol, 0.06 equiv) were added. After 10 min, 3-methylbut-3-enylbenzene (73 mg, 0.50 mmol, 1.00 equiv) and tert-butyl hydroperoxide (5.5 M solution in decane, 25 μL, 0.14 mmol, 0.28 equiv) were added followed by a second portion of EtOH (0.5 mL). Finally TMDSO (182 μL, 1.00 mmol, 2.00 equiv) was added and the resulting homogeneous dark-brown reaction mixture was stirred at r.t. and monitored by TLC (hexane–Et₂O, 40:1). Upon completion, the reaction was quenched with H₂O (0.5 mL). Sat. aq NaHCO₃ (3 mL) and brine (2 mL) were added and the reaction mixture was extracted with Et₂O (5 × 10 mL). The solvent was removed under reduced pressure (40 mbar, 40 °C) and the crude product was purified by flash chromatography (hexane–Et₂O, 40:1) to afford 3-azido-3-methylbutylbenzene (3e; 94 mg, 99%) as a pale-yellow liquid. All the spectroscopical data were consistent with those previously reported.¹¹

Typical Procedure B

4-Azidosulfonylbenzoic acid (5; 176 mg, 0.75 mmol, 1.50 equiv) was suspended in EtOH (2 mL) at r.t. under argon. Et₃N (101 μL, 0.715 mmol, 1.43 equiv) was added and the mixture was stirred until the mixture became clear colorless solution (15–20 min). Co(BF₄)₂·6H₂O (10 mg, 0.03 mmol, 0.06 equiv) and ligand 2 (14 mg, 0.03 mmol, 0.06 equiv) were added. After 10 min, 3-methylbut-3-enylbenzene (73 mg, 0.50 mmol, 1.00 equiv) and tert-butyl hydroperoxide (5.5 M solution in decane, 25 μL, 0.14 mmol, 0.28 equiv) were added followed by a second portion of EtOH (0.5 mL). Finally TMDSO (182 μL, 1.00 mmol, 2.00 equiv) was added and the resulting homogeneous dark-brown reaction mixture was stirred at r.t. and monitored by TLC (hexane–Et₂O, 40:1). Upon completion, the reaction was quenched with H₂O (0.5 mL). Sat. aq NaHCO₃ (3 mL) and brine (2 mL) were added and the reaction mixture was extracted with Et₂O (5 × 10 mL). The solvent was removed under reduced pressure (40 mbar, 40 °C) and the crude product was purified by flash chromatography (hexane–Et₂O, 40:1) to afford 3-azido-3-methylbutylbenzene (3e; 94 mg, 99%) as a pale-yellow liquid. All the spectroscopical data were consistent with those previously reported.¹¹
13C NMR (CDCl3, 75 MHz): δ = 169.72, 135.58, 128.55, 128.30, 66.49, 59.49, 45.56, 26.21.

MS (ESI): m/z = 256.2 [M + Na].


3-Azido-3-methyl-N-phenylbutanamide (3b)

Rf = 0.11 (hexane–EtOAc, 2:1).

IR: 3252 (m), 3131 (w), 3071 (w), 2972 (w), 2096 (s), 1654 (s), 1539 (s), 1438 (s), 1341 (m), 1237 (s), 1107 (w), 972 (w), 804 (w), 851 (w), 739 (s) cm−1.

1H NMR (CDCl3, 300 MHz): δ = 7.83 (br s, 1 H, NH), 7.53–7.51 (m, 2 H, ArH), 7.14–7.09 (m, 1 H, ArH), 4.07–3.91 (m, 2 H, OCH2), 1.46 [s, 9 H, C(CH3)3], 1.32 (s, 6 H, 2 N3CCH3), 1.30 (s, 3 H, N3CCH3).

13C NMR (CDCl3, 75 MHz): δ = 172.92, 155.04, 79.89, 71.11, 59.86, 49.26, 28.26, 23.15, 18.43.

MS (ESI): m/z = 256.24 [M + Na].


Acknowledgment

This research was supported by a Swiss National Science Foundation grant. The authors thank Sigma–Aldrich for providing all the azide sources.

References


Tertiary Azides from α,α-Disubstituted Olefins


(13) Co(BF₄)₂·6H₂O (6 mol%), ligand 2 (6 mol%), alkene (0.5 mmol), azide source (1.5 mmol), t-BuOOH (30 mol%), TMDSO (1 mmol), EtOH (2.5 mL).

(14) All sulfonyl azides tested in the reaction were provided by Sigma–Aldrich.