# Zirconium Sulfophenyl Phosphonate as a Heterogeneous Catalyst in the Preparation of β-Amino Alcohols from Epoxides

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A convenient method for the ring opening of epoxides by aromatic amines, catalysed by zirconium sulfophenyl phosphonate in solvent-free conditions, is described.

## Introduction

The ring opening of epoxides by amines is an important route for the preparation of β-amino alcohols.[1,2] Vicinal amino alcohols are a common structural component in a vast group of natural products and synthetic molecules with biological and pharmaceutical activity.[3] A number of examples of such ring opening reactions have been reported in recent years, including the regioselective ring opening of epoxides at high temperature with an excess of amine[4] or in the presence of a catalyst in homogeneous conditions.[5] Although a wide choice of products is available many are associated with one or other drawbacks, especially the need for an excess of reagents, reflux temperatures and sluggish reactions. Recently, microwave irradiation has been used for this purpose, either without a catalyst,[6] or in the presence of Montmorillonite K-10 clay as a catalyst[7] with aliphatic amines in solvent-free conditions.

Surface-mediated solid-phase reactions are of growing interest due to their ease of set-up, mild reaction conditions, rapid reaction, selectivity, increased yields, high purity of compounds and low cost compared with their homogeneous counterparts.[8]

Based on our previous experience in the use of zirconium sulfophenyl phosphonate[9] as a heterogeneous catalyst in organic chemistry,[10] we found that this acidic catalyst is an excellent promoter for the conversion of epoxides into the corresponding 1,2-amino alcohols (Figure 1).

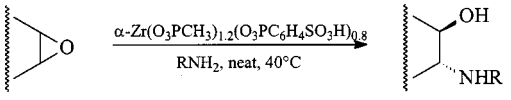


Figure 1. General scheme of 1,2-amino alcohol formation

## Results and Discussion

Initially we studied the reactivity of aliphatic and aromatic amines using cyclohexene oxide as a model substrate. The reaction takes place in the solid phase at 40 °C with 2 mmol of amine and 1 mmol of cyclohexene oxide in the presence of 50 mg of the catalyst. Under these conditions, cyclohexene oxide reacts with both aliphatic and aromatic amines, but high yields are achieved only with aromatic amines. The low yield obtained using aliphatic amines can be explained by an interaction of the catalyst with the more basic nitrogen, resulting either in a proton exchange reaction or intercalation.[11] Consequently we focused our attention only on aromatic amines with various epoxides. All the experimental results are summarized in Table 1.

With the present method, even sterically hindered amines such as *o*-methoxy- and 2,5-dimethylaniline (entry 4 and 8), which are known to undergo the reaction only at 80 °C,[12] react under mild conditions in good yield.

It is important to note that in the case of terminal epoxides (entries 13−17), the main product obtained, of the two possible regioisomers, was formed by the attack of the amine at the terminal carbon. This regioselectivity is probably due to the steric hindrance of aromatic amines that attack the less-hindered carbon of the epoxide. Only for the reaction of styrene oxide with aniline (entry 16) did we observe a reverse regioselectivity towards the regioisomer in which the attack of the amine at the benzylic carbon was preferred. The β-amino alcohols obtained using cycloalkene oxides were shown to posses a *trans* configuration by $^1$H NMR spectroscopy (see Exp. Sect.).

The method described here is a new entry into the ring opening of epoxides and the use of zirconium sulfophenyl phosphonate represents the first example of an aminohydroxylation using aromatic amines in heterogeneous catalysis; it compares favourably, and represents a valid alternative, to the existing methods. To summarize the present procedure has two important features: (i) its simplicity: the reactions are carried out with no solvent and under mild conditions; products are recovered by simple workup; (ii) the recyclable nature of the catalyst[16] whose preparation does not require any particular skill.[9]

## Experimental Section

**General Method:** $^1$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC 200 spectrometer operating at

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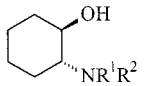
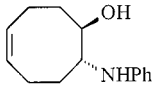
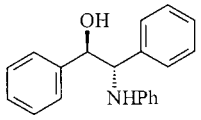
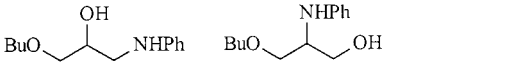
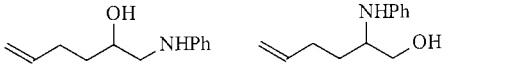
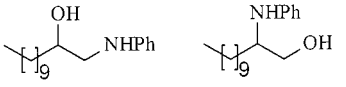
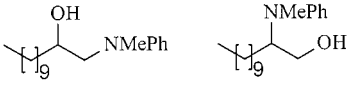
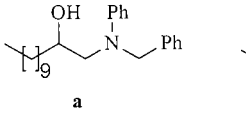
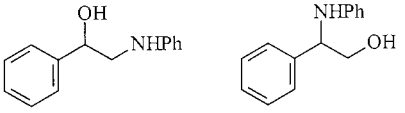
  1434−193X/01/1121−4149 $ 17.50+.50/0 

Table 1. Ring opening of epoxides by amines mediated by zirconium sulfophenyl phosphonate

| Entry | | Amino alcohols | Time [h] | Yield [%] | Ref. |
|---|---|---|---|---|---|
| 1 | **1a** |  $R^1$=H; $R^2$=cyclohexyl- | 24 | 17 | |
| 2 | **1b** | $R^1$=H; $R^2$=*n*-butyl- | 24 | 36 | |
| 3 | **1c** | $R^1$=H; $R^2$=Phenyl- | 20 | 92 | [13] |
| 4 | **1d** | $R^1$=H; $R^2$=2-methoxyphenyl- | 22 | 90 | |
| 5 | **1e** | $R^1$=H; $R^2$=4-methoxyphenyl- | 2 | 68 | [12] |
| 6 | **1f** | $R^1$=H; $R^2$=2-hydroxyphenyl- | 20 | 92 | [13] |
| 7 | **1g** | $R^1$=H; $R^2$=4-bromophenyl- | 4 | 68 | |
| 8 | **1h** | $R^1$=H; $R^2$=2,5-dimethylphenyl- | 22 | 91 | |
| 9 | **1i** | $R^1$=H; $R^2$=4-nitrophenyl- | 20 | 70 | [13] |
| 10 | **1j** | $R^1$=Me; $R^2$=Phenyl- | 20 | 54 | [13] |
| 11 | **2** |  | 24 | 74[a] | [13] |
| 12 | **3** |  | 48 | 73[a] | [14] |
| 13 | **4** |  **a** **b** (Ratio of **a**:**b** = 8:1) | 19 | 94[b] | |
| 14 | **5** |  **a** **b** (Ratio of **a**:**b** = 6:1) | 24 | 81[c] | |
| 15 | **6** |  **a** **b** (Ratio of **a**:**b** = 7:1) | 21 | 72[c] | |
| 16 | **7** |  **a** **b** (Ratio of **a**:**b** = 9:1) | 4 | 64[a,c] | [13] |
| 17 | **8** |  **a** **b** (Ratio of **a**:**b** = 9:1) | 24 | 58[a,c] | |
| 18 | **9** |  **a** **b** Ratio of **a**:**b** = 1:8) | 24 | 83[c] | **8a**[5] **8b**[15] |

[a] Carried out at 60 °C. – [b] Overall yield of inseparable mixture of products, ratio was determined by GC-MS measurement. – [c] Overall yield of purified compounds (see Exp. Sect.).

200.1 and 50.53 MHz, respectively, in the Fourier transform mode. GC analyses and MS spectra were carried out with an HP 5890 gas chromatograph (dimethyl silicone column 12.5 m) equipped with an HP 5971 Mass Selective Detector. Melting points were measured with Microthermal apparatus and are uncorrected. Flash column chromatography was performed on 0.040−0.063 mm (230−400 mesh ASTM) Merck silica gel. Elemental analysis were performed on a Carlo Erba Model 1106 elemental analyzer.

**General Procedure:** α-$Zr(O_3PCH_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$ (50 mg/mmol epoxide) was added to a stirred mixture of epoxide (1 mmol) and amine (2 mmol) at 40 °C under nitrogen. Stirring was continued until TLC indicated that the epoxide was no longer present. The mixture was then diluted with dichloromethane and filtered on a Buckner funnel. Concentration of the filtrate under reduced pressure gave a residue that was purified by chromatography on silica gel using the eluent indicated in each case.

***trans*-2-(Cyclohexylamino)cyclohexan-1-ol (1a):** Eluent: dichloromethane/EtOAc (4:1). Yield: 17%, white solid, m.p. 88−90 °C. – $^1$H NMR: δ = 0.96−1.43 (m, 9 H), 1.57−1.87 (m, 6 H), 1.88−2.16 (m, 3 H), 2.35 (ddd, *J* = 11.2, 9.8, 4.1 Hz, 1 H), 2.64 (m, 1 H), 3.17 (ddd, *J* = 9.8, 9.6, 4.9 Hz, 1 H). – $^{13}$C NMR: δ = 24.3, 24.6, 25.1, 25.3, 26.0, 31.2, 33.1, 33.2, 34.9, 53.4, 60.4, 73.6. – GC-MS: *m*/*z*: = 197, 168, 154, 138, 114. – $C_{12}H_{23}NO$ (197.3): calcd. C 73.04, H 11.75, N 7.1; found C 73.18, H 11.6, N 7.02.

***trans*-2-(Butylamino)cyclohexan-1-ol (1b):** Eluent: dichloromethane/EtOAc (4:1). Yield: 36%, yellow oil. − $^1$H NMR: δ = 0.94 (t, *J* = 7.3 Hz, 3 H), 0.98 (m, 1 H), 1.20−1.52 (m, 7 H), 1.74 (m, 2 H), 2.08 (m, 2 H), 2.20 (ddd, *J* = 11.3, 9.5, 3.9 Hz, 1 H), 2.46 (ddd, *J* = 11.5, 6.6, 6.6 Hz, 1 H), 2.78 (ddd, *J* = 11.0, 6.9, 6.9 Hz, 1 H), 3.15 (ddd, *J* = 9.4, 9.4, 3.8 Hz,1 H). − $^{13}$C NMR: δ = 14.3, 20.8, 24.9, 25.3, 30.6, 32.8, 34.1, 46.7, 63.9, 73.7. − GC-MS: *m*/*z* = 171, 142, 128, 112. − $C_{10}H_{21}NO$ (171.2): calcd. C 70.12, H 12.36, N 8.18; found C 70.2, H 12.41, N 8.07.

***trans*-2-(2-Methoxyanilino)cyclohexan-1-ol (1d):** Eluent: hexane/EtOAc (9:1). Yield 90%, pale grey solid, m.p. 75−77 °C. − $^1$H NMR: δ = 1.1 (m, 1 H), 1.38 (m, 3 H), 1.78 (m, 2 H), 2.13 (m, 2 H), 2.96 (br. s, 2 H, NH e OH), 3.17 (ddd, *J* = 11.3, 9.2, 4.0 Hz, 1 H), 3.45 (ddd, *J* = 10.6, 9.4, 4.6 Hz, 1 H), 3.86 (s, 3 H), 6.65−6.93 (m, 5 H). − $^{13}$C NMR: δ = 24.7, 25.5, 31.0, 33.6, 55.8, 60.0, 75.0, 110.2, 111.8, 117.7, 121.7.138.0, 147.9. − GC-MS: *m*/*z* = 221, 178, 162, 149, 136. − $C_{13}H_{19}NO_2$ (221.3): calcd. C 70.56, H 8.65, N 6.33; found C 70.31, H 8.56, N 6.45.

***trans*-2-(4-Bromoanilino)cyclohexan-1-ol (1g):** Eluent: hexane/EtOAc (9:1). Yield: 68%, pale yellow solid, m.p. 125−127 °C. − $^1$H NMR: δ = 1.01 (m, 1 H), 1.28 (m, 3 H), 1.60 (m, 2 H), 2.04 (m, 2 H), 3.03 (ddd, *J* = 11.4, 9.7, 4.1 Hz, 1 H), 3.30 (ddd, *J* = 10.2, 10.2, 4.4 Hz, 1 H), 6.54 (d, *J* = 10.4 Hz, 2 H), 7.20 (d, *J* = 10.4 Hz, 2 H). − $^{13}$C NMR: δ = 24.2, 24.9, 31.5, 33.2, 60.2, 74.5, 109.8, 115.8, 132.0, 146.7. − GC-MS: *m*/*z* = 271, 270, 240, 226, 210, 147, 134. − $C_{12}H_{16}BrNO$ (270.1): calcd. C 53.35, H 5.97, N 5.18; C 53.26, H 6.11, N 5.28.

***trans*-2-(2,5-Dimethylanilino)cyclohexan-1-ol (1h):** Eluent: hexane/EtOAc (9:1). Yield: 91%, yellow oil. − $^1$H NMR: δ = 1.09 (m, 1 H), 1.39 (m, 3 H), 1.77 (m, 2 H), 2.11 (s, 3 H), 2.15 (m, 2 H), 2.30 (s, 3 H), 3.22 (ddd, *J* = 9.4, 11.1, 4.0 Hz, 1 H), 3.43 (ddd, *J* = 9.5, 9.5, 4.1 Hz, 1 H), 6.53 (d, *J* = 7.2 Hz, 1 H), 6.62 (s, 1 H), 6.96 (d, *J* = 7.2 Hz, 1 H). − $^{13}$C NMR: δ = 17.7, 22.0, 24.8, 25.5, 32.4, 33.7, 60.3, 75.0, 112.9, 119.0, 120.5, 130.7, 137.2, 146.1. − GC-MS: *m*/*z* = 219, 176, 160, 145, 132. − $C_{14}H_{21}NO$ (219.3): calcd. C 76.67, H 9.65, N 6.39; found C 76.83, H 9.7, N 6.18.

***trans*-2-Anilino-1,2-diphenylethan-1-ol (3):** Eluent: hexane/EtOAc (9:1). Yield: 73%, white solid, m.p. 121−123 °C.[14] − $^1$H NMR:[14] δ = 2.34 (br. s, 1 H), 4.52 (br. s, 1 H), 4.72 (d, *J* = 4.8 Hz, 1 H), 5.11 (d, *J* = 4.8 Hz, 1 H), 6.58 (m, 2 H), 6.72 (m, 1 H), 7.25 (m, 12 H). − $^{13}$C NMR: δ = 63.7, 77.2, 113.9, 117.9, 127.6, 127.9, 128.0, 128.2, 128.3, 129.1, 138.5, 140.0, 146.8. − GC-MS: *m*/*z* = 289, 182, 104, 77. − $C_{20}H_{19}NO$ (289.3): calcd. C 83.01, H 6.62, N 4.84; found C 83.23, H 6.51, N 4.76.

**1-Anilino-3-butoxy-2-propanol (4a) and 2-Anilino-3-butoxy-1-propanol (4b):** Eluent: hexane/EtOAc (9:1). Inseparable mixture of **4a** and **4b** (8:1), yield 94%, yellow oil.
**4a:** $^1$H NMR: δ = 0.95 (t, *J* = 7.1 Hz, 3 H), 1.41 (m, 2 H), 1.59 (m, 2 H), 2.6 (br. s, 1 H, OH), 3.16 (dd, *J* = 12.7, 6.9 Hz, 1 H), 3.32 (dd, *J* = 12.7, 4.3 Hz, 1 H), 3.53 (m, 4 H), 4.04 (m, 1 H), 6.71 (m, 3 H), 7.19 (m, 2 H). − $^{13}$C NMR: δ = 14.0, 19.4, 31.7, 46.9, 69.1, 71.5, 73.2, 113.3, 117.7, 129.3, 148.4. − GC-MS: *m*/*z* = 223, 136, 106, 93, 77.
**4b:** GC-MS: *m*/*z* = 223, 148, 132, 120, 106, 91.

**1-Anilino-5-hexen-2-ol (5a):** Eluent: dichloromethane/EtOAc (49:1). Yield: 70%, pale yellow solid, m.p. 41−42 °C. − $^1$H NMR: δ = 1.65 (m, 2 H), 2.23 (m, 2 H), 3.04(dd, *J* = 12.7, 8.6 Hz, 1 H), 3.29 (dd, *J* = 12.7, 3.9 Hz, 1 H), 3.88 (m, 1 H), 4.96−5.17 (m, 2 H), 5.87 (m, 1 H), 6.72 (m, 3 H), 7.19 (m, 2 H). − $^{13}$C NMR: δ = 30.0, 34.1, 50.2, 68.8, 113.4, 115.2, 117.9, 129.4, 138.2, 148.3. − GC-MS: *m*/*z* = 191, 132, 118, 106, 77. − $C_{12}H_{17}NO$ (191.2): calcd. C 75.35, H 8.96, N 7.32; found C 75.28, H 9.02, N 7.29.

**2-Anilino-5-hexen-1-ol (5b):** Eluent: dichloromethane/EtOAc (49:1), Yield: 11%, yellow oil. − $^1$H NMR: δ = 1.67 (m, 2 H), 2.12 (m, 2 H), 3.55 (m, 2 H), 3.78 (m, 1 H), 4.95−5.16 (m, 2 H), 5.85 (m, 1 H), 6.71 (m, 3 H), 7.18 (m, 2 H). − $^{13}$C NMR: δ = 30.4, 31.2, 54.5, 64.2, 113.7, 115.3, 117.8, 129.4, 138.1, 147.8. − GC-MS: *m*/*z* = 191, 160, 118, 77. − $C_{12}H_{17}NO$ (191.2): calcd. C 75.35, H 8.96, N 7.32; found C 75.44, H 8.92, N 7.33.

**1-Anilino-2-dodecanol (6a):** Eluent: hexane/EtOAc (9:1). Yield: 63%, white solid, m.p. 46−48 °C. − $^1$H NMR: δ = 0.9 (t, *J* = 7.1 Hz, 3 H), 1.13−1.68 (m, 18 H), 3.01 (dd, *J* = 12.8, 8.5 Hz, 1 H), 3.27 (dd, *J* = 12.8, 3.2 Hz, 1 H), 3.84 (m, 1 H), 6.71 (m, 3 H), 7.19 (m, 2 H). − $^{13}$C NMR: δ = 14.2, 22.7, 25.7, 29.4, 29.7, 32.0, 35.2, 50.3, 70.4, 113.3, 117.9, 129.3, 148.3. − GC-MS: *m*/*z* = 277, 246, 136, 106. − $C_{18}H_{31}NO$ (277.4): calcd. C 77.92, H 11.26, N 5.05; found C 77.78, H 11.37, N 5.18.

**2-Anilino-1-dodecanol (6b):** Eluent: hexane/EtOAc (9:1). Yield: 9%, pale yellow oil. − $^1$H NMR: δ = 0.89 (t, *J* = 7.1 Hz, 3 H), 1.18−1.63 (m, 18 H), 3.50 (m, 2 H), 3.78 (m, 1 H), 6.71 (m, 3 H), 7.20 (m, 2 H). − $^{13}$C NMR: δ = 14.5, 23.1, 26.6, 29.7, 29.9, 30.0, 30.1, 32.3, 32.6, 55.8, 64.9, 114.2, 118.3, 129.7, 148.2. − GC-MS: *m*/*z* = 277, 246, 136, 106. − $C_{18}H_{31}NO$ (277.4): calcd. C 77.92, H 11.26, N 5.05; found C 77.86, H 11.31, N 5.12.

**1-[Benzyl(phenyl)amino]dodecan-2-ol (8a):** Eluent: hexane/EtOAc (9:1). Yield: 52%, yellow oil. − $^1$H NMR: δ = 0.93 (t, *J* = 7.0 Hz, 3 H), 1.22−1.67 (m, 18 H), 2.05 (br. s, 1 H, OH), 3.35 (dd, *J* = 14.7, 9.1 Hz, 1 H), 3.55 (dd, *J* = 14.7, 3.2 Hz, 1 H), 4.01 (m, 1 H), 4.69 (s, 2 H), 6.65−6.89 (m, 3 H), 7.18−7.44 (m, 7 H). − $^{13}$C NMR: δ = 14.6, 23.2, 26.2, 29.8, 31.1, 30.1, 30.2, 32.4, 35.2, 55.9, 58.8, 70.1, 113.8, 117.8, 127.2, 127.3, 129.1, 129.7, 138.9, 149.5. − GC-MS: *m*/*z* = 197, 183, 167, 106, 91, 77. − $C_{25}H_{37}NO$ (367.57): calcd. C 81.69, H 10.15, N 3.81; found C 81.42, H 10.01, N 3.97.

**2-[Benzyl(phenyl)amino]dodecan-1-ol (8b):** Eluent: hexane/EtOAc (9:1). Yield: 6%, yellow oil. − $^1$H NMR: δ = 0.94 (t, *J* = 7.1 Hz, 3 H), 1.16−1.74 (m, 18 H), 3.71 (m, 2 H), 4.07 (m, 1 H), 4.48 (s, 2 H), 6.75−6.95 (m, 3 H), 7.16−7.43 (m, 7 H). − $^{13}$C NMR: δ = 14.6, 23.1, 27.3, 29.6, 29.7, 29.9, 30.0, 30.1, 32.3, 48.6, 62.4, 63.9, 115.9, 118.5, 127.1, 127.2, 129.1, 129.5, 140.1, 150.4. − GC-MS: *m*/*z* = 212, 197, 183, 106, 91, 77. − $C_{25}H_{37}NO$ (367.57): calcd. C 81.69, H 10.15, N 3.81; found C 81.56, H 10.1, N 3.95.

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[1] D. M. Hodgson, A. R. Gibbs, G. P. Lee, *Tetrahedron* **1996**, *25*, 14361−14384.
[2] S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561−2576.
[3] [3a] G. A. Rogers, S. M. Parsons, D. C. Nilsson, L. M. Bahr, W. D. Kornreich, R. Kaufman, R. S. Jacobs, B. Kirtman, *J. Med. Chem.* **1989**, *32*, 1217−1230. − [3b] B. L. Chng, A. Ganesan, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1511−1514.
[4] [4a] J. A. Deyrup, C. L. Moher, *J. Org. Chem.* **1969**, *34*, 175−179. − [4b] P. A. Crooks, R. Szyudler, *Chem. Ind. (London)* **1973**, 1111−1112.
[5] S. Rampalli, S. S. Chaudhari, K. G. Akamanchi, *Synthesis* **2000**, *1*, 78−80 and references cited.

[6] U. M. Lindström, B. Olofsson, P. Somfai, *Tetrahedron Lett.* **1999**, *40*, 9273−9276.
[7] M. M. Mojtadei, M. R. Saidi, M. Bolourtchion, *J. Chem. Res. (S)* **1999**, 128−129.
[8] G. W. Kobalka, R. M. Pagni, *Tetrahedron* **1997**, *53*, 7999−8065 and references cited therein.
[9] M. Curini, O. Rosati, E. Pisani, U. Costantino, *Synlett.* **1996**, 333−334.
[10] [10a] M. Curini, M. C. Marcotullio, O. Rosati, E. Pisani, U. Costantino, *Synlett.* **1997**, 769−770. − [10b] M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati, U. Costantino, *Tetrahedron Lett.* **1998**, *39*, 8159−8162. − [10c] M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati, U. Costantino, *Synthetic Comm.* **1999**, 541−546.
[11] To support this proposal, in a separate experiment we used the catalyst previously treated with an excess of *n*-butylamine, filtered and dried at 120 °C for 12 hours. Treatment of cyclohexene oxide with aniline under standard reaction conditions with this form of catalyst lead to no reaction even after 24 hours.
[12] L. Rajender Reddy, M. Arjun Reddy, N. Bhanumathi, K. Rama Rao, *Synlett* **2000**, *3*, 339−340.
[13] G. Sekar, V. K. Singh, *J. Org. Chem.* **1999**, *64*, 287−289.
[14] B. Alcaide, C. López-Mardomingo, R. Pérez-Ossorio, J. Plumet, *J. Chem. Soc., Perkin Trans. 2* **1983**, 1649−1653.
[15] J. Barluenga, L. Alonso-Cires, G. Asensio, *Synthesis* **1981**, 376−378.
[16] The catalyst can be reused several times after washing with dichloromethane and drying at 120 °C for 12 hours. The reaction of cyclohexene oxide and aniline (entry 3) has been repeated three times with the following yields: 87% (24 h), 88% (24 h), 85% (24 h).

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