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A practical synthesis of *N*-aryl-substituted oxazolidinone-containing ketone catalysts for asymmetric epoxidation

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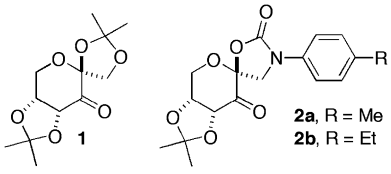
Abstract—*N*-Aryl-substituted oxazolidinone-containing ketone catalysts for the asymmetric epoxidation of olefins can be efficiently prepared from D-glucose and anilines.

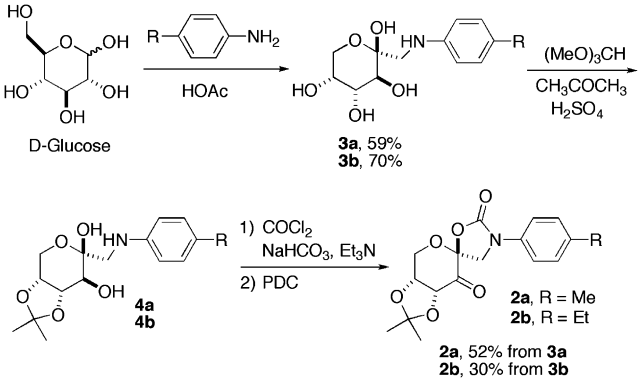
1. Introduction

Dioxiranes generated in situ from chiral ketones are effective for the asymmetric epoxidation of olefins.[1] In our earlier studies, we have shown that fructose-derived ketone **1** gives high ee's for trans- and trisubstituted olefins (Scheme 1).[2] Subsequently, we have found that *N*-aryl substituted oxazolidinone-containing ketones **2a** and **2b**, readily prepared from D-glucose and *p*-toluidine or 4-ethylaniline, provide high ee's for substrates such as cis-olefins,[3] styrenes,[4] and certain trisubstituted and tetrasubstituted olefins,[5] which are not effective with ketone **1**. While our original procedure for the synthesis of ketone **2** is suitable for small scale, operational drawbacks such as column chromatography purification make large-scale ketone synthesis less convenient (Scheme 2). Considering that these ketone catalysts could potentially be useful, efforts have been made to further improve their synthesis so that large quantities of ketone catalysts can be readily obtained.



Scheme 1.

The original and improved syntheses of ketones **2a**[3a] and **2b**[4] are outlined in Schemes 2 and 3, respectively. In the original procedure, the ketalization of aminoalcohol **3** was achieved with $(MeO)_3CH$ and H_2SO_4 in acetone. Aminodiol **4** was isolated as an oil after neutralization with NH_4OH. Extensive vacuum pumping of compound **4** is required to remove all of the water contained in ammonium hydroxide, which is harmful to the phosgene cyclization. In addition, the isolated compound (**4**) is contaminated with small amounts of impurities from the ketalization reaction (amounts of impurities are highly dependent on how well the reaction is monitored). Consequently, column chromatography is required after phosgene cyclization to ensure product purity, which is highly undesirable for a large-scale operation. However, it was observed that a large amount of white solid precipitated during the ketalization, and the white solid was found to be hydrogen sulfate salt **5**, which could be obtained in good yield by simple filtration. The impurity previously encountered could easily be removed by washing with ether. It was also found that using the less expensive dimethoxypropane (DMP) in place of $HC(OMe)_3$ further improved the ketalization and caused **5** to efficiently crystallize in the



Scheme 2. Original syntheses of ketones **2a** and **2b**.

Keywords: Asymmetric epoxidation; Chiral dioxirane; Chiral ketone.
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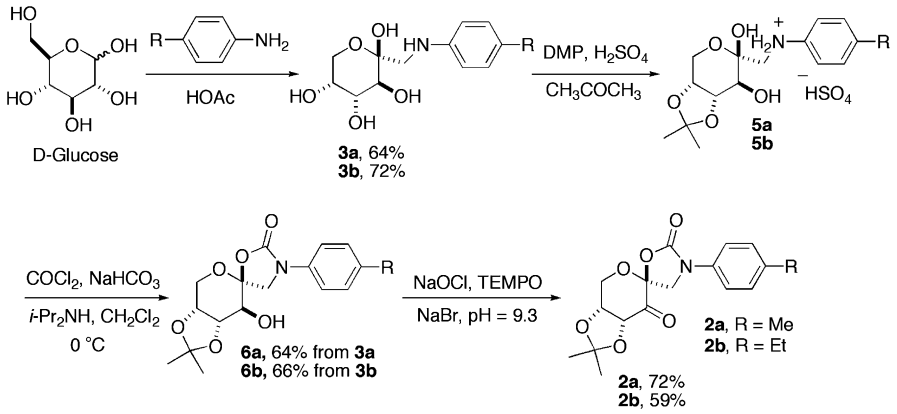
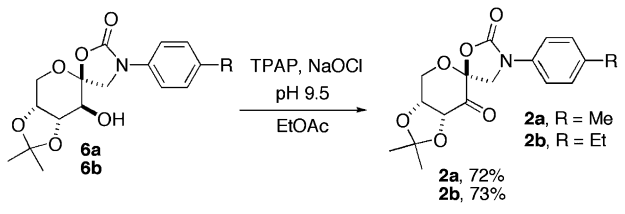


Scheme 3. Improved syntheses of ketones **2a** and **2b**.

reaction mixture. Therefore, the isolation of salt **5** instead of oil **4** is highly beneficial.

Salt **5** was then directly used for neutralization and phosgene cyclization. Subjecting salt **5** to the previous reaction conditions ($NaHCO_3$, phosgene, followed by Et_3N)[4] resulted in low yield. However, the reaction was much cleaner if additional base such as diisopropylamine was added.[6] Diisopropylamine could possibly act as a proton shuttle between the insoluble salt **5** and solid $NaHCO_3$. The formed oxazolidinone **6** can be isolated by recrystallization or can be used directly in the oxidation step without isolation.

In the previous procedure, the oxidation was accomplished using PDC as oxidizing agent. To further improve this step, various other oxidation methods, such as $RuCl_3 \cdot xH_2O$–$NaIO_4$,[7a] $Py \cdot SO_3$–DMSO,[7b] Ac_2O–DMSO,[7c] TEMPO–Oxone,[7d] and TEMPO–bleach[7e] were briefly investigated. Among these oxidation methods, TEMPO–bleach system was found to be the best choice overall. After much experimentation, it was found that a catalytic amount of TEMPO (1.5%) with bleach as the primary oxidant yielded ketone **2** in good yield after recrystallization of the final product. It was found that the choice of solvent and reaction pH are very important for this transformation.[8] The oxidation proceeded efficiently at pH 9.3 in a mixture of CH_2Cl_2 and toluene (5:1). Finally, a similar TPAP–bleach oxidation procedure was also found to yield ketone **2** in good yield and purity (Scheme 4).[9] Catalysts prepared by the improved synthetic pathway were found to give comparable epoxidation results to ketones prepared by the original sequence using Oxone as oxidant.



Scheme 4.

In summary, we report a practical synthesis of *N*-aryl-substituted oxazolidinone-containing ketone catalysts for asymmetric epoxidation of olefins from D-glucose and anilines in four steps. The process described is operationally simpler when compared to the original procedure and can easily produce the desired ketone catalysts in large quantities.

2. Experimental

2.1. Synthesis of ketone 2a

To a mixture of D-glucose (270.0 g, 1.5 mol), *p*-toluidine (192.9 g, 1.8 mol), and water (51.4 mL) was added HOAc (1.62 g, 0.027 mol). The mixture was rotated on a rotary evaporator (sealed without vacuum) at 90–93 °C for 2 h (during this time the product precipitated from the reaction mixture). After cooling to room temperature, ether–ethanol (3:1, 1600 mL) was added. Upon stirring at room temperature for an additional 2 h, the mixture was filtered, washed with ether (2×400 mL), ether–ethanol (5:1, 420 mL), ether (2×400 mL), and dried under vacuum to give aminoalcohol **3a** as a white solid (259.4 g, 64%).[10]

To a mixture of aminoalcohol **3a** (161.4 g, 0.6 mol) and 2,2-dimethoxypropane (222.0 mL, 1.8 mol) in acetone (1400 mL) with stirring (using mechanical stirrer) under Ar at 0 °C was added concd H_2SO_4 (48.0 mL, 0.86 mol) via addition funnel over 45 min. After stirring at 0 °C for an additional 1.5 h (the white solid product precipitated in the reaction mixture over the course of the reaction), ether (150 mL) was added. The mixture was filtered, washed with acetone–ether (1:4, 3×350 mL), ether (350 mL), and dried under vacuum for 2–3 h to give salt **5a** as a white solid (220.2 g, 90%) (Compound **5a** should be used immediately for the next step. Exhaustive vacuum drying and/or prolonged storage could lead to decomposition). IR (NaCl, film): 3364 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 7.15–7.07 (m, 5H), 6.40 (br s, 3H), 4.22 (d, J=5.7 Hz, 1H), 4.12–4.02 (m, 2H), 3.87 (d, J=13.5 Hz, 1H), 3.47 (d, J=7.5 Hz, 1H), 3.44–3.35 (m, 1H), 3.30–3.16 (m, 1H), 2.25 (s, 3H), 1.40 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 137.0, 135.9, 130.1, 121.9, 107.9, 95.1, 76.1, 73.0, 70.6, 59.4, 56.5, 28.1, 26.4, 20.7. Anal. Calcd for $C_{16}H_{25}NO_9S$: C, 47.17; H, 6.18; N, 3.44; S, 7.87. Found: C, 47.05; H, 6.04; N, 3.60; S, 8.11.

A mixture of salt **5a** (220.2 g, 0.54 mol) and $NaHCO_3$ (403.2 g, 4.8 mol) in CH_2Cl_2 (1000 mL) was stirred (using

mechanical stirrer) under Ar at 0 °C for 1 h. Diisopropylamine (30.3 g, 0.3 mol) was then added. Upon stirring at 0 °C for 30 min, phosgene (20% solution in toluene, 377 mL, 0.71 mol) was added via addition funnel over 5.3 h. After stirring at 0 °C for an additional 1.5 h, the cold bath was removed. The reaction mixture was stirred overnight, filtered, and washed with satd $NaHCO_3$ (200 mL), water (2×200 mL), brine (200 mL), dried (Na_2SO_4), filtered, concentrated to about 300 mL, and filtered to give **6a** as white solid (104.5 g). The filtrate was concentrated and recrystallized from hexane–CH_2Cl_2 (3:1, 200 mL) to give an additional 24.9 g of **6a** (combined yields, 72%). IR (NaCl, film): 3400, 1761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J=8.4 Hz, 2H), 7.15 (d, J=8.4 Hz, 2H), 4.37–4.26 (m, 4H), 4.14 (d, J=13.5 Hz, 1H), 3.81–3.78 (m, 2H), 2.91 (s, 1H), 2.32 (s, 3H), 1.57 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 135.0, 134.3, 129.7, 118.8, 110.0, 100.9, 76.7, 73.3, 71.7, 62.0, 53.3, 28.4, 26.3, 21.1. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.61; H, 6.16; N, 4.35.

To a mixture of alcohol **6a** (30.2 g, 0.09 mol) and NaBr (9.26 g, 0.09 mol) in CH_2Cl_2–toluene (5:1, 360 mL) at 0 °C was added TEMPO (0.215 g, 0.0014 mol). Recently purchased 5% NaOCl (270 mL, adjusted to pH 9.3 by $NaHCO_3$)[11] was added with vigorous stirring (using mechanical stirrer) over 2.5 h (during the addition, the internal temperature of the reaction mixture was kept at 4–8 °C, and the reaction was monitored by GC). The layers of the reaction mixture were separated, and the aqueous phase was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were washed with satd $Na_2S_2O_3$ (2×200 mL), water (6×100 mL), dried (Na_2SO_4), filtered through a pad of silica gel (40 g), and washed with EtOAc (200 mL). The filtrate was concentrated to ca. 20 mL. Upon addition of hexane (500 mL), the mixture was shaken until the viscous residue solidified and precipitated. Filtration and recrystallization (90 mL, EtOAc and 30 mL, hexane) gave ketone **2a** as an off white solid (21.7 g, 72%). IR (NaCl, film): 1773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J=8.4 Hz, 2H), 7.20 (d, J=8.4 Hz, 2H), 4.88 (d, J=5.1 Hz, 1H), 4.75 (d, J=10.5 Hz, 1H), 4.66–4.62 (m, 2H), 4.27 (d, J=13.5 Hz, 1H), 3.76 (d, J=10.5 Hz, 1H), 2.35 (s, 3H), 1.50 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 151.2, 134.7, 134.5, 129.8, 118.8, 111.1, 99.2, 77.6, 75.6, 61.1, 50.0, 27.3, 26.2, 21.0. Anal. Calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.18; H, 5.86; N, 4.22.

In an another run, alcohol **6a** was used for oxidation directly without isolation described as follows:

A mixture of salt **5a** (186.0 g, 0.45 mol) and $NaHCO_3$ (336.0 g, 4.0 mol) in CH_2Cl_2 (1200 mL) was stirred (using mechanical stirrer) under N_2 at 0 °C for 1 h. Diisopropylamine (25.3 g, 0.25 mol) was then added. Upon stirring at 0 °C for 10 min, phosgene (20% solution in toluene, 310 mL, 0.58 mol) was added via addition funnel over 5 h. The reaction mixture was warmed to room temperature and stirred overnight, filtered, and washed with CH_2Cl_2 (3×200 mL). The filtrate was washed with satd $NaHCO_3$ (700 mL) and water (2×700 mL). The solution was used directly in the next step.

To the above solution was added CH_2Cl_2 (500 mL) and NaBr (51.5 g, 0.50 mol). After cooling to 0 °C, TEMPO (1.17 g, 0.0075 mol) was added, followed by freshly purchased 5% NaOCl (1400 mL, adjusted to pH 9.3 by $NaHCO_3$)[11] with vigorous stirring (using mechanical stirrer) over 4 h (during the addition, the internal temperature of the reaction mixture was kept at 4–8 °C, the reaction was monitored by GC). After stirring for an additional 3 h at the same temperature, the layers of the reaction mixture were separated. The organic layers were washed with satd $Na_2S_2O_3$ (3×300 mL), water (5×250 mL), dried (Na_2SO_4), filtered through a pad of silica gel (d=9.5 cm, h=0.6 cm), washed with EtOAc (500 mL), and concentrated to 80–100 mL. Upon addition of hexane (800 mL), the mixture was vigorously shaken until the viscous residue solidified and precipitated. Filtration and recrystallization (250 mL, EtOAc and 200 mL, hexane) gave ketone **2a** as pale yellow solid (80.0 g). The mother liquor was concentrated and recrystallized (200 mL, EtOAc and 70 mL, hexane) to give ketone **2a** as yellow solid (15.0 g) (total 95.0 g, combined yields, 63% over two steps).

2.2. Synthesis of ketone 2b

To a mixture of D-glucose (270.0 g, 1.5 mol), 4-ethylaniline (218.1 g, 1.8 mol), and water (51.4 mL) was added HOAc (1.62 g, 0.027 mol). The mixture was rotated on a rotary evaporator (sealed without vacuum) at 90–93 °C for 70 min (during this time the product precipitated from the reaction mixture). After cooling to room temperature, ether–ethanol (3:1, 1600 mL) was added. Upon stirring at room temperature for an additional 2 h, the mixture was filtered, washed with ether (2×400 mL), ether–ethanol (5:1, 420 mL), ether (2×400 mL), and dried under vacuum to give aminoalcohol **3b** as a white solid (303.5 g, 72%).[10]

To a mixture of aminoalcohol **3b** (169.8 g, 0.6 mol) and 2,2-dimethoxypropane (222.0 mL, 1.8 mol) in acetone (1400 mL) while stirring (using mechanical stirrer) under Ar at 0 °C was added concd H_2SO_4 (48.0 mL, 0.86 mol) via addition funnel over 45 min. After stirring at 0 °C for an additional 1.5 h (the white solid product precipitated in the reaction mixture over the course of the reaction), ether (400 mL) was added. The mixture was filtered, washed with acetone–ether (1:4, 3×350 mL), ether (350 mL), and dried under vacuum for 2–3 h to give salt **5b** as a white solid (202.1 g, 80%) (Compound **5b** should be used immediately for the next step. Exhaustive vacuum drying and/or prolonged storage could lead to decomposition). IR (NaCl, film): 3349 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 8.09 (m, 4H), 7.24 (m, 4H), 4.23 (dd, J=5.7, 2.1 Hz, 1H), 4.15–4.01 (m, 2H), 3.90 (d, J=13.2 Hz, 1H), 3.49 (d, J=7.2 Hz, 1H), 3.43 (d, J=12.3 Hz, 1H), 3.27 (d, J=12.3 Hz, 1H), 2.58 (q, J=7.8 Hz, 2H), 1.41 (s, 3H), 1.28 (s, 3H), 1.16 (t, J=7.8 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 143.0, 136.2, 128.9, 121.8, 107.9, 95.2, 76.1, 73.0, 70.6, 59.4, 56.4, 28.1, 27.8, 26.4, 15.7. Anal. Calcd for $C_{17}H_{27}NO_9S$: C, 48.45; H, 6.46; N, 3.32; S, 7.61. Found: C, 48.65; H, 6.60; N, 3.33; S, 7.62.

A mixture of salt **5b** (202.1 g, 0.48 mol) and $NaHCO_3$ (403.2 g, 4.8 mol) in CH_2Cl_2 (1000 mL) was stirred (using mechanical stirrer) under Ar at 0 °C for 1 h. Diisopropylamine (30.3 g, 0.30 mol) was then added. Upon stirring at

0 °C for 30 min, phosgene (20% solution in toluene, 377 mL, 0.71 mol) was added via addition funnel over 5.3 h. After stirring at 0 °C for an additional 1.5 h, the cold bath was removed. The reaction mixture stirred overnight, filtered, and washed with satd $NaHCO_3$ (200 mL), water (2×200 mL), brine (200 mL), dried (Na_2SO_4), filtered, concentrated to about 300 mL, and filtered to give **6b** as white solid (116.2 g). The filtrate was concentrated and recrystallized from hexane–CH_2Cl_2 (3:1, 260 mL) to give an additional 22.6 g of **6b** (combined yields, 83%). IR (NaCl, film): 3400, 1761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J=8.4 Hz, 2H), 7.19 (d, J=8.4 Hz, 2H), 4.39–4.26 (m, 4H), 4.15 (d, J=13.5 Hz, 1H), 3.83–3.80 (m, 2H), 2.96 (br s, 1H), 2.63 (q, J=7.8 Hz, 2H), 1.57 (s, 3H), 1.40 (s, 3H), 1.22 (t, J=7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 140.5, 135.1, 128.4, 118.8, 109.8, 101.1, 76.4, 73.3, 71.4, 61.8, 53.3, 28.4, 28.2, 26.2, 15.8. Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.93; H, 6.65; N, 4.03.

To a mixture of alcohol **6b** (31.4 g, 0.09 mol) and NaBr (9.26 g, 0.09 mol) in CH_2Cl_2–toluene (5:1, 360 mL) at 0 °C was added TEMPO (0.215 g, 0.0014 mol). Freshly purchased 5% NaOCl (270 mL, adjusted to pH 9.3 by $NaHCO_3$)[11] was added with vigorous stirring (using mechanical stirrer) over 2.5 h (during the addition, the internal temperature of the reaction mixture was kept at 4–8 °C. The reaction was monitored by GC). The layers of the reaction mixture were separated, and the aqueous phase was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were washed with satd $Na_2S_2O_3$ (2×200 mL), water (6×100 mL), dried (Na_2SO_4), filtered through a pad of silica gel (40 g), washed with EtOAc (250 mL), and concentrated to ca. 20 mL. Upon addition of hexane (500 mL), the mixture was shaken until the viscous residue solidified and precipitated. Filtration and recrystallization (30 mL, EtOAc and 30 mL, hexane) gave ketone **2b** as an off white solid (18.4 g, 59%). IR (NaCl, film): 1773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J=8.4 Hz, 2H), 7.19 (d, J=8.4 Hz, 2H), 4.85 (d, J=5.4 Hz, 1H), 4.71 (d, J=10.8 Hz, 1H), 4.64–4.56 (m, 2H), 4.23 (d, J=13.2 Hz, 1H), 3.72 (d, J=10.5 Hz, 1H), 2.61 (q, J=7.5 Hz, 2H), 1.46 (s, 3H), 1.40 (s, 3H), 1.20 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 151.2, 141.0, 134.6, 128.5, 118.8, 111.0, 99.1, 77.7, 75.5, 61.0, 50.0, 28.3, 27.2, 26.1, 15.7. Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.48; H, 6.19; N, 4.06.

In an another run, alcohol **6b** was used for oxidation directly without isolation described as follows:

A mixture of salt **5b** (191.0 g, 0.45 mol) and $NaHCO_3$ (336.0 g, 4.0 mol) in CH_2Cl_2 (1200 mL) was stirred (using mechanical stirrer) under N_2 at 0 °C for 1 h. Diisopropylamine (25.3 g, 0.25 mol) was then added. Upon stirring at 0 °C for 10 min, phosgene (20% solution in toluene, 310 mL, 0.58 mol) was added via addition funnel over 5 h. The reaction mixture was warmed to room temperature and stirred overnight, filtered, and washed with CH_2Cl_2 (3×200 mL). The filtrate was washed with satd $NaHCO_3$ (700 mL) and water (2×700 mL). The solution was used directly for the next step.

To the above solution was added CH_2Cl_2 (500 mL) and NaBr (51.5 g, 0.50 mol). Upon cooling to 0 °C, TEMPO (1.17 g, 0.0075 mol) was added, followed by recently purchased 5% NaOCl (1400 mL, adjusted to pH 9.3 by $NaHCO_3$)[11] with vigorous stirring (using mechanical stirrer) over 4 h (during the addition, the internal temperature of the reaction mixture was kept at 4–8 °C, the reaction was monitored by GC). After stirring for an additional 3 h at the same temperature, the layers of the reaction mixture were separated. The organic layers were washed with satd $Na_2S_2O_3$ (3×300 mL), water (5×250 mL), dried (Na_2SO_4), filtered through a pad of silica gel (d=13.0 cm, h=1.4 cm), washed with EtOAc (800 mL), concentrated, and recrystallized (120 mL, EtOAc and 300 mL, hexane) to give ketone **2b** as a pale yellow solid (87.0 g). The mother liquor was concentrated and recrystallized (20 mL, EtOAc and 30 mL, hexane) to give ketone **2b** as brown solid (12.0 g) (total 99.0 g, combined yields, 63% over two steps).

2.3. General procedure for TPAP–NaOCl oxidation

To the solution of alcohol **6** (for **6a**: 50.3 g; for **6b**: 52.4 g, 0.15 mol) in EtOAc (375 mL), was added 0.1 M $NaHCO_3$–Na_2CO_3 buffer (pH=9.5, 495 mL)[12] followed by TPAP (0.53 g, 0.0015 mol). After stirring at room temperature for 10 min, recently purchased NaOCl (5%, 450 mL) was then added dropwise at rt over 4 h (reaction followed by GC). The mixture was then filtered through Celite and washed with EtOAc until no product came out. After separating the layers, the aqueous phase was extracted with EtOAc (2×150 mL). The combined organic layers were washed with water (2×150 mL), brine (150 mL), dried (Na_2SO_4), concentrated, and recrystallized from ethyl acetate–hexane (3:1, 200 mL for **2a**; 1:1, 120 mL for **2b**) to give the ketone **2** as a white solid (35.9 g, 72% for **2a**; 38.0 g, 73% for **2b**).

Acknowledgements

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6. Other bases such as *tert*-butylamine, pyridine, 2,6-lutidine, imidazole, ammonium hydroxide, and ammonia (gas) were also tested. Among these bases, *tert*-butylamine worked well.
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8. The reaction was examined from pH 9.0 to 12.8 with 1% TEMPO in CH_2Cl_2. The optimal conversion was obtained around pH 9.3. Various solvents were also tested for the reaction. The conversions in these solvents (1.5% TEMPO at pH 9.3, for 4 h) are as following: acetone (<1%), EtOAc (6%), EtOAc–dioxane (1:1, v/v) (23%), EtOAc–DME (1:1, v/v) (27%), EtOAc–CH_3CN (1:1, v/v) (67%), EtOAc–CH_2Cl_2 (4:1, v/v) (44%), EtOAc–CH_2Cl_2 (2:1, v/v) (82%), EtOAc–CH_2Cl_2 (1:1, v/v) (94%), CH_2Cl_2 (>99%), and $PhCH_3$–CH_2Cl_2 (1:5, v/v) (>99%). The amount of solvent can be reduced when $PhCH_3$–CH_2Cl_2 (1:5, v/v) (10 mL per gram of substrate) is used when compared to CH_2Cl_2 (20 mL per gram of substrate).
9. For leading references on TPAP–NaOCl oxidation, see: (a) Gonsalvi, L.; Arends, I. W. C. E.; Sheldon, R. A. *Org. Lett.* **2002**, *4*, 1659; (b) Gonsalvi, L.; Arends, I. W. C. E.; Moilanen, P.; Sheldon, R. A. *Adv. Synth. Catal.* **2003**, *345*, 1321.
10. Hodge, J. E.; Fisher, B. E. *Methods Carbohydr. Chem.* **1963**, *2*, 99.
11. NaOCl used was freshly purchased from Alfa (5%). Low conversion was obtained if poor quality NaOCl used. The control on pH of NaOCl solution is also very important for the oxidation. The pH was adjusted to 9.3 by addition of solid $NaHCO_3$ (carefully monitored by pH meter, ~24 mg $NaHCO_3$/mL NaOCl).
12. The buffer was prepared by mixing 0.1 M $NaHCO_3$ and 0.1 M Na_2CO_3 until pH 9.5 as monitored by the pH meter.