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Asymmetric synthesis of 3-hydroxyl-2-alkanones via tandem organocatalytic aminoxylation of aldehydes and chemoselective diazomethane homologation

Li Yang [a,b], Run-Hua Liu [a], Bing Wang [a,*], Ling-Ling Weng [c], Hu Zheng [c]

[a] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China
[b] State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China
[c] Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, China

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ABSTRACT

Asymmetric synthesis of 3-hydroxyl-2-alkanones is achieved via one-pot, tandem organocatalytic aminoxylation of aldehydes and chemoselective CH_2N_2-induced homologation. Accelerating effect of water is observed in α-aminoxylation. $MgCl_2$, a Lewis acid additive, improves the chemoselectivity of the diazomethane homologation to 6:1 in favor of ketone.

Optically active α-hydroxyketones (acyloins) are versatile intermediates in organic synthesis (Fig. 1). For example, they are potential precursors to chiral 1,2-diols and 1,2-aminoalcohols, which are common structural features found in numerous chiral ligands, auxiliaries, and biologically active compounds.[1] However, methods for the asymmetric synthesis of this type of compounds are rather limited. Notable examples include Rubottom–type oxidation of ketone-derived enolates by Davis' oxazirine reagent,[2] asymmetric epoxidation followed by hydrolysis,[3] and Sharpless asymmetric dihydroxylation of enol ethers.[4] However, the level of stereocontrol in these protocols is very sensitive toward the structure of substrates, and varies widely (68% up to 95% ee). In addition, pre-formation of enolate or its equivalent is required, which not only raises the issue of regioselectivity for non-symmetric substrates, but also excludes the presence of many base-sensitive functions. On the other hand, organocatalysis has made enormous progress in the past decade,[5] and highly enantioselective organocatalytic α-aminoxylation of aldehydes using nitrosobenzene has been developed.[6] The products have been utilized in subsequent reduction,[6] Horner–Wadsworth–Emmons olefination,[7] and allylation[8] reactions in a tandem manner to afford diverse chiral building blocks. Although ketones also undergo such α-aminoxylation,[9] a survey of the literature revealed that open-chain non-symmetric ketones were generally not ideal substrates, as the chemoselectivity was undermined by α-hydroxyamination, and the regioselectivity was low.[9b] Consequently, direct α-aminoxylation of ketones, at its present stage, cannot provide an efficient and general access to chiral non-cyclic α-hydroxyketones.[10] As our continuing interest in vicinally functionalized chiral alcohol and amines,[11] we envisioned that an alternative tandem aldehyde aminoxylation–homologation sequence could circumvent such limitations, and would afford the desired 3-hydroxyl-2-alkanones with a wider substrate scope. Herein we describe the preliminary results of this study.

The tandem sequence was investigated step by step, first with the aminoxylation using 3-phenylpropanal **1a** as a model substrate. Surprisingly, this was not as smooth as we expected. It was found that in dry DMSO (re-distilled from CaH_2, and stored over 4 Å MS under Ar), the reaction was considerably slower than that reported, and after reductive treatment ($NaBH_4$/EtOH/0 °C),

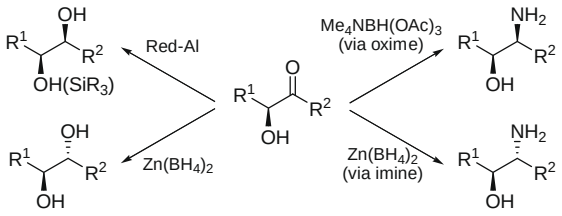

Figure 1. Selected synthetic utilities of chiral α-hydroxy ketones.

* Corresponding author. Tel./fax: +86 21 54237570.
E-mail address: wangbing@fudan.edu.cn (B. Wang).

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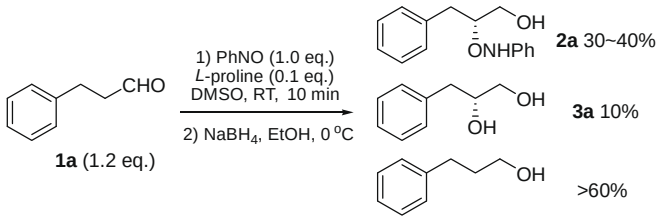


Scheme 1. Preliminary results using anhydrous DMSO.

large amounts of 3-phenylpropanol were formed. The yield of the expected product **2a** was only 30–40% after extended reaction time,[12] along with up to 10% of **3a** which might result from the decomposition of **2a** (Scheme 1). Shifting to other organocatalysts[6e,13] or solvents ($CHCl_3$ and MeCN) did not improve the results. On the other hand, when we accidentally used DMSO from an old bottle, both the reaction rate and the yield were significantly improved. This prompted us to examine the effect of water[14] more closely than that revealed in the literature (Table 1).

The water content of our re-distilled DMSO was determined to be 0.02% by Karl Fischer method, while that of the unfresh solvent was ~2.2%. It turned out that water did accelerate the reaction, and 1.0% (v/v) water in DMSO was optimal, providing the highest reaction rate and yield (entry 3). The solvent effect was especially pronounced in the range below 1.0%, where less water corresponded to slower reaction and unpredictable yields (entries 1–3). Presumably, the dependence on water was due to that it facilitated the hydrolysis of the iminium salt intermediate to α-aminoxyaldehyde, regenerating the proline catalyst. Although initial enamine formation produced 1 equiv of water, it seemed that this was not sufficient to maintain a smooth catalytic cycle and certain amounts of added water were required. Interestingly, this has not been noted in previous reports. Thus DMSO containing 1.0% water was used throughout our subsequent study.

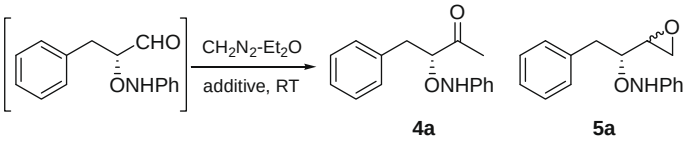
The next step was homologation of aldehyde to methyl ketone. Schlotterbeck and Arndt have reported this transformation via reaction with diazomethane.[15a,b] However, the literature precedences also indicated that the chemoselectivity was profoundly influenced by the structure of the parent aldehydes, those bearing eletron-withdrawing α-substituents tend to give the undesired epoxide.[15b] In our preliminary trial, when the α-aminoxyaldehyde was treated in situ with an ethereal solution of CH_2N_2, the desired ketone **4a** was obtained along with equimolar epoxide **5a** in low yields (23%). Indeed, compared with unbranched aldehydes, the α-aminoxy substitution did exhibit a significant adverse effect. Lowering the reaction temperature only aggrevated the situation, with an even lower yield of **4a** and worse selectivity (entry 2). Inspired by Yamamoto's Lewis acid–catalyzed homologation,[16] we turned our attention to simple Lewis acid additives in an attempt to overcome the unfavorable intrinsic preference for epoxide (Table 2). The use of borontrifluoride etherate led to intractable mixtures, while lanthanides afforded only moderate ketone to epoxide ratio (entries 3 and 4). To our delight, anhydrous magnesium salts

Table 1
Effect of water in proline-catalyzed α-aminoxylation

Entry	H_2O% (v/v)	Time (min)	**2a** (%)	ee[a] (%)
1	0.02[b]	40	30–40	98
2	0.2[c]	20	50	98
3	1.0[c]	5	64	98
4	2.2[b]	10	60	98
5	10.0[c]	10	60	98

[a] Determined by chiral HPLC.
[b] Determined by Karl Fischer method.
[c] Obtained by adding calculated amounts of water to dry DMSO.

Table 2
Effect of Lewis acid in CH_2N_2-induced rearrangement



4a **5a**

Entry	Additive	**4a**[a] (%)	ee[b] (%)	**5a** (%)	dr[c] (%)
1	None	23	97	23	1.2:1
2[d]	None	13	Nd	40	Nd
3	MeOH	17	95	35	1.1:1
4	$BF_3{\cdot}OEt_2$	0	–	0	–
5	$CeCl_3$	30	Nd	17	Nd
6	$MgCl_2$	60	97	10	1.2:1
7	$MgBr_2$	50	97	16	Nd

[a] Isolated yields for two steps.
[b] Determined by chiral HPLC.
[c] Determined by NMR, relative stereochemistry not assigned.
[d] Reaction run at −10 °C.

increased the chemoselectivity to a useful level of 6:1 with enhanced yields of ketone (up to 60%). Protic additive (MeOH) showed the opposite selectivity, favoring the epoxide. Thus inexpensive $MgCl_2$ was chosen as the key modulator to be introduced before addition of CH_2N_2.

The role of $MgCl_2$ could be rationalized as outlined in Figure 2. The metal counterion trapped the alkoxide anion, so that only the lone pair electron of the oxygen, rather than a negative charge, could be used to displace N_2. Thus path B was considerably impeded, while path A, which involved 1,2-hydrogen shift, was unaffected.

With the optimized conditions in hand, the tandem aminoxylation–homologation of various aldehydes was examined (Table 3). The sequential reactions were carried out conveniently in one pot, without isolation of the intermediates, in moderate to good yields over two steps.[17] β-Branched aldehyde showed slightly better yields (entry 6). β-Alkylthio substitution was well tolerated (entry 7). Finally, ω-oxygenated aldehydes were also suitable substrates, providing the opportunity for further elaboration. The ee's of all products were excellent, indicating that no racemization occurred during the CH_2N_2-induced rearrangement. The absolute configuration of the product was established by single-crystal X-ray diffraction of compound **4b** (Fig. 3).[18]

Synthetic application of the 3-phenylaminoxyl-2-alkanone products was demonstrated by a highly enantioselective synthesis of compound **9** (Scheme 2), the C12–C21 chiral building block for Epothilones.[19] The *N–O* bond in *ent*-**4h** was easily cleaved by $CuSO_4$ in MeOH or hydrogenolysis (H_2, cat. PtO_2). The crude alcohol was protected with TBS to afford the known ketone **6** (70%). Wittig olefination constructed the tri-substituted double bond in a highly stereoselective manner, and selective removal of the terminal TBS protection afforded **9** (85%). Chiral HPLC analysis of alcohol **9** confirmed that its optical purity was almost completely preserved (97% ee).[20] In our hands, this is a more convenient route with higher ee, compared with other methods such as enzymatic resolution (88–90% ee) or asymmetric allylation (90–95% ee).

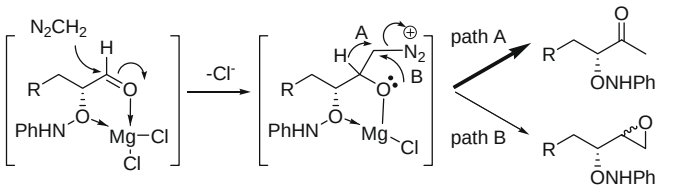
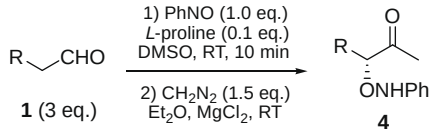
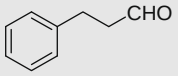
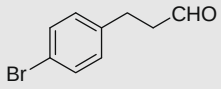
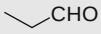
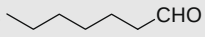
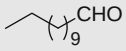
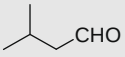
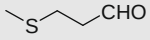
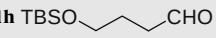
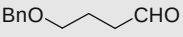


Figure 2. Plausible role of Mg(II) additives.

Table 3
One-pot tandem α-aminoxylation and regioselective CH_2N_2-induced rearrangement



Entry	1	Ketone 4,[a] (%)	ee[b] (%)
1	**1a** 	**4a**, 60	97
2	**1b** 	**4b**, 57	98
3	**1c** 	**4c**, 40	97
4	**1d** 	**4d**, 46	98
5	**1e** 	**4e**, 46	98
6	**1f** 	**4f**, 55	98
7	**1g** 	**4g**, 43	97
8	**1h** 	**4h**, 42	99
9	**1i** 	**4i**, 41	95

[a] Isolated yields for two steps.
[b] Determined by chiral HPLC.

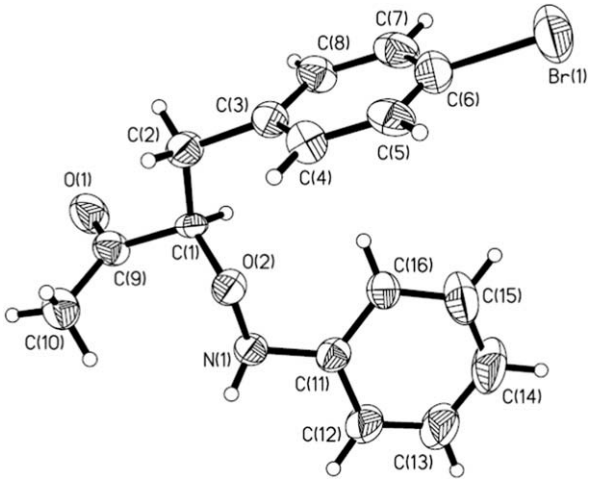
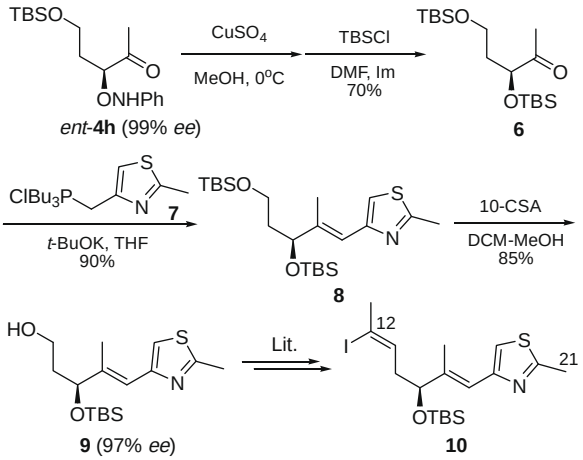


Figure 3. X-ray structure of **4b**.



Scheme 2. Synthesis of a chiral building block (**9**) for Epothilone.

In summary, we have developed a general method for the synthesis of 3-hydroxyl-2-alkanones via tandem organocatalytic aminoxylation of aldehydes and chemoselective diazomethane homologation. An accelerating effect of water was observed for the aminoxylation, while $MgCl_2$ served as an effective Lewis acid additive for the chemoselective homologation of α-aminoxyaldehyde to ketone. A key intermediate for the synthesis of Epothilones was prepared using this approach in high ee. Studies on chemoselective epoxide formation and utilization of this byproduct via regioselective C–2 ring-opening of the epoxide are under investigation.

Acknowledgments

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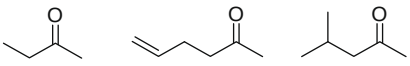
10. Only the following three examples of open-chain non-symmetric ketone have been reported to give meaningful results so far, see Ref. 9c.



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17. *General procedures*: To a solution of L-proline (12 mg, 0.1 mmol) in DMSO–H_2O (99:1) were added PhNO (107 mg, 1.0 mmol) and aldehyde (3 mmol) successively under fast stirring. After the color of the solution turned into orange, $MgCl_2$ (~500 mg) was added, followed by CH_2N_2 (10 mL, 0.5–0.6 M in Et_2O), and the mixture was stirred at rt for 2 h, purged with N_2, quenched with aq NH_4Cl, and diluted with ether (50 mL). The aqueous phase was extracted with ether (2×50 mL), the combined organic layer was dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography. Compound **4a**: $[\alpha]_D^{24}$ +63.7 (*c* 0.80, $CHCl_3$) for 98% ee; HPLC: Chiralpak AD-H column; detected at 214 nm; eluent: *n*-hexane/2-propanol = 80/20 (v/v), flow rate: 0.7 ml/min, t_1 = 11.2 min (minor), t_2 = 14.6 min (major); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3H), 2.98 (AB-d, 1H, J_{AB} = 14.1, J = 9.0 Hz), 3.10 (AB-d, 1H, J_{AB} = 14.1, J = 4.2 Hz), 4.56 (dd, J = 9.3, 4.2 Hz), 6.65 (d, 2H, J = 7.8 Hz), 6.91(t, 2H, J = 7.5 Hz), 7.15 (t, 2H, J = 8.1 Hz), 7.23–7.38 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.8, 36.9, 89.4, 114.5, 122.4, 127.0, 128.7, 128.9, 129.6, 136.6, 147.8, 208.7 ppm; HR-MS Calcd for $C_{16}H_{17}NO_2$ 255.1259. Found 255.1265. Compound **4d**: $[\alpha]_D^{27}$ +54.6 (*c* 0.85, $CHCl_3$) for 97.9% ee; HPLC: Chiralcel OD column; detected at 214 nm; eluent: *n*-hexane/2-propanol = 95/5 (v/v), flow rate: 0.8 ml/min, t_1 = 8.63 min (minor), t_2 = 9.28 min (major); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3H, J = 6.6 Hz), 1.27–1.41 (m, 4H), 1.60–1.43 (m, 2H), 1.70–1.80 (m, 2H), 2.20 (s, 3H), 4.36 (t, 1H, J = 6.0 Hz), 6.91–7.00 (m, 3H), 7.27 (t, 2H, J = 7.8 Hz), 7.37 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8, 22.2, 25.0, 25.7, 30.2, 30.4, 88.5, 114.4, 122.1, 128.7, 128.7, 147.9, 209.1 ppm; HR-MS (ESI) Calcd for $C_{14}H_{22}NO_2$ 236.1645, Found 236.1645. Compound **4h**: $[\alpha]_D^{24}$ +53.6 (*c* 1.36, $CHCl_3$) for 99% ee; HPLC: Chiralpak AD-H column; detected at 214 nm; eluent: *n*-hexane/2-propanol = 95/5 (v/v), flow rate: 0.7 ml/min, t_1 = 8.7 min (minor), t_2 = 17.7 min (major); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.84–2.08 (m, 2H), 2.21 (s, 3H), 3.76–3.94 (m, 2H), 4.61 (dd, 1H, J = 8.4, 4.2 Hz), 6.94–7.00 (m, 3H), 7.22–7.30 (m, 2H), 7.41 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.4,−5.3, 18.3, 25.9, 26.3, 33.5, 58.7, 85.3, 114.6, 122.4, 128.9, 148.0, 208.9 ppm.
18. Crystallographic data for **4b** ($C_{16}H_{16}BrNO_2$): T = 293(2) K; wavelength: 0.71073 Å; crystal system: monoclinic; space group: *C*2; unit cell dimensions: a = 32.049(16) Å, b = 5.537(3) Å, c = 8.889(4) Å, α = 90°, β = 90°, γ = 90°; V = 1576.6(13) Å^3; Z = 4; ρ_{calcd} = 1.408 Mg/m^3; F(000) = 680; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0454, wR_2 = 0.1145; R indices (all data), R_1 = 0.0740, wR_2 = 0.1430; 3306 reflections measured, 2480 were unique ($R_{(int)}$ = 0.0400). CCDC 719767 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
19. For reviews on the synthesis of Epothilones, see: (a) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2014; (b) Zhang, R.; Liu, Z. *Curr. Org. Chem.* **2004**, *8*, 267.
20. *Compound* **9**: $[\alpha]_D^{22}$ −28.6 (*c* 0.39, $CHCl_3$) for 97% ee; HPLC: Chiralcel OD column; detected at 230 nm; eluent: *n*-hexane/2-propanol = 80/20 (v/v), flow rate: 0.7 ml/min, t_1 = 6.3 min (major), t_2 = 14.5 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.75–1.95 (m, 2H), 2.02 (s, 3H), 2.32 (br s, 1H), 2.72 (s, 3H), 3.76 (m, 2H), 4.40 (dd, 1H, J = 6.9, 4.5 Hz), 6.53 (s, 1H), 6.94 (s, 1H).