Asymmetric Catalysis

Direct Catalytic Enantioselective α-Aminoxylation of Ketones: A Stereoselective Synthesis of α-Hydroxy and α,α′-Dihydroxy Ketones**

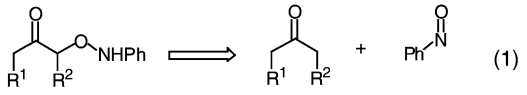
*Anders Bøgevig, Henrik Sundén, and Armando Córdova**

One of the ultimate goals and challenges in chemistry is to develop catalytic stereoselective transformations for the creation of optically active molecules from simple and easily available starting materials.[1] Optically active α-hydroxy carbonyl moieties are commonly found in numerous important natural products. This has led to extensive research to find new diastereoselective and enantioselective routes for their syntheses.[2] One way of preparing these compounds is the asymmetric α-hydroxylation of enolates.[3] Despite extensive research in this area it was not until recently that Yamomoto et al. reported a more efficient catalytic system based on AgX/binap complexes (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl), which mediate indirect α-oxidation of activated tin enolates.[4]

1a

Asymmetric reactions catalyzed by metal-free organic catalysts have received increased attention in recent years.[5] Interestingly, following the discovery of amino acid catalyzed stereoselective Robinson annulations in the early 1970s,[6] there was no intensive research on this concept for other C–C bond-forming reactions for several decades even though the reaction is frequently used to prepare building blocks in natural products synthesis.[7] It was not until recently that researchers demonstrated that amino acid derivatives function as catalysts for direct asymmetric intermolecular reactions.[8–16]

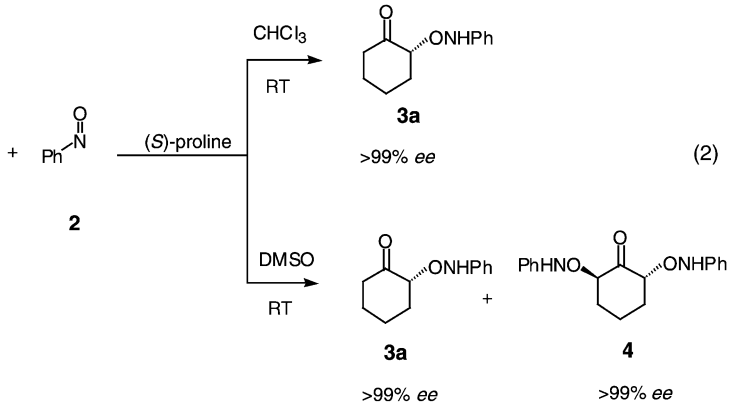
Based on the elegant work of Yamomoto et al. and our previous research on amine-catalyzed asymmetric synthesis, we envisioned that an amino acid could catalyze the α-oxyamination of unmodified ketones [Eq. (1)].[4,8d,f,g,i,9b–9g,10a,10c] We believed that the enhanced Brønstedt basicity of the nitrogen atom would favor O-addition over N-addition. Hence, we embarked on the quest to develop a novel enamine-catalyzed asymmetric route for the synthesis of α-hydroxy-containing molecules.[17]



(1)

Herein, we present a method for the direct catalytic α-oxidation of ketones. This new transformation yields protected α-hydroxy ketones with excellent regioselectivity and >99% *ee*. In addition, unsubstituted cyclic ketones were α,α′-dioxylated with remarkable high selectivity affording the corresponding C_2-symmetric ketodiols in >99% *ee*.

In an initial experiment, we treated cyclohexanone (**1a**) (10 mmol) with nitrosobenzene (**2**) (1 mmol) in the presence



(2)

of a catalytic amount of (*S*)-proline (20 mol%) in $CHCl_3$ (4 mL) at room temperature [Eq. (2)]. The initial light blue solution changed first to light green, then to dark green, and finally to orange within 30 min. The reaction was quenched after 2 h, and NMR analysis of the crude product revealed that no starting material remained and only α-aminooxylated ketone **3a** had formed. Most satisfying we could not observe the N-addition product, and ketone **3a** was isolated in 91% yield and >99% *ee* as determined by chiral HPLC analysis. The reactions also proceed with only two equivalents of cyclohexanone and 10 mol% of the catalyst.

Next, we tested a number of solvents (THF, $CHCl_3$, dimethylformamide (DMF), Et_2O, *N*-methylpyrrolidinone (NMP), toluene, dimethyl sulfoxide (DMSO), CH_3CN, and neat) for the proline-catalyzed α-aminoxylation with **1a** as the donor and found that the best solvents with regard to the reactivity of proline were $CHCl_3$ and DMSO. In all cases tested, the corresponding product **3a** was isolated with >95% *ee*. For example, the reaction in DMSO was complete within 30 min providing not only ketone **3a** in 70% yield and >99% *ee* but also the corresponding C_2-symmetric α,α′-diaminoxy ketone **4** in 22% yield and >99% *ee*. The formation of **4** could be circumvented by slow addition of **3a** (1M solution in DMSO) with a syringe pump to the reaction mixture. The second O-addition exhibited remarkable selectivity, since no *meso*-diol adduct was detected either by NMR or HPLC analyses during the course of the reaction. This is the first time that this type of double stereoselective nucleophilic attack to an electrophile has been reported in a

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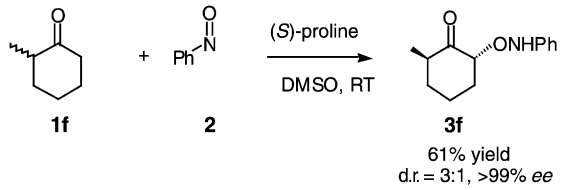
proline-catalyzed reaction, which indicates that nitrosobenzene is more reactive and/or provides less steric hindrance than other electrophiles such as diazocarboxylates or α-imino glyoxylates.[9,10]

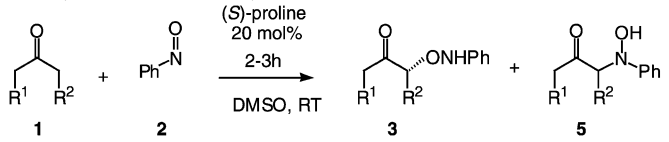
Next, we performed the corresponding reaction with a set of different aliphatic ketones (Table 1). The reactions were effective, and the corresponding α-aminoxy ketones **3a**–**3e** were isolated in good yield with >99% *ee*.[18] In addition, excellent regioselectivities were observed for α-aminoxylation of acyclic ketones and no α,α′-diaminoxylated ketones were observed. The oxidation occurred exclusively on the methylene carbon of the ketones. For example, protected hydroxy ketone **3b** was isolated as a single regioisomer in 70% yield with >99% *ee*. With regards to the O- or N-selectivity of the reaction, we found that the reaction was chemoselective, furnishing no N-addition products for transformations with cyclic ketones as donors. However, α-aminoxylation of acyclic ketones afforded small amounts (<25%) of the corresponding 2-aminated ketones **5** with the same regioselectivity as the O-addition adducts with a minor chiral induction.

Furthermore, the sterically hindered, racemic 2-methylcyclohexanone **1f** was also efficiently α- aminoxylated oxyaminated, providing the corresponding keto adduct **3f** as a 3:1 mixture of diastereomers (*trans/cis*) in >99% *ee* (Scheme 1). In this case, excellent O-selectivity was observed since no N-addition product was observed. The reactions were readily performed on gram scale in not strictly anhydrous solvents and in the presence of air. In addition, the progress of the reaction can be monitored simply by the human eye since the reaction mixture changes colors from light blue to green and finally to orange when the reaction is complete.



Scheme 1. Direct catalytic asymmetric synthesis of **3f**.

Table 1: Proline-catalyzed direct α-aminoxylation of different ketones.[a]

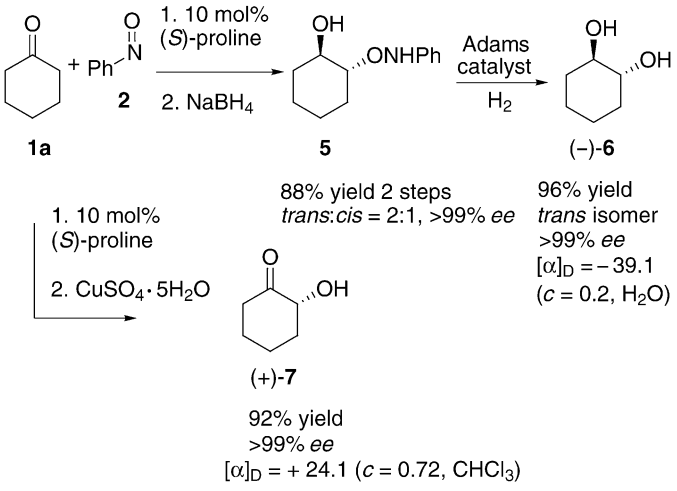


Entry	Ketone	R^1	R^2	Yield [%][b]	**3**:**5**	*ee* [%] of **3**[c]	*ee* [%] of **5**[c]
1	**1a**		$-(CH_2)_3-$	70	>100/1	>99	–
				(91)[d]	(>100/1)[d]	(>99)[d]	–
2	**1b**	H	Me	93	81:19	>99	11
3	**1c**	Et	Me	66	98:2	99	7
4	**1d**	H	$CH_2CH{=}CH_2$	87	8:22	>99	n.d.[e]
5	**1e**	H	*i*Pr	64	90:10	>99	n.d.[e]

[a] Experimental conditions: A mixture of **1** (10 mmol, 10 equiv), **2** (1 mmol), and (*S*)-proline was stirred at room temperature for 2–3 h. The crude product obtained after aqueous workup was purified by column chromatography. [b] Combined yield of isolated products after silica gel column chromatography. [c] Determined by chiral-phase HPLC analyses. [d] The reaction was performed in $CHCl_3$. [e] Not determined.

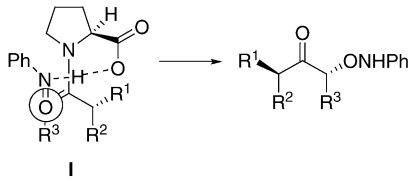
As selective reduction of α-hydroxy ketones to both *syn*- and *anti*-1,2-diols is known, the present procedure is one practical route for the preparation of all the possible stereoisomers of chiral 1,2-diols. In addition, the ketones **3a** and **4** were readily deprotected with $CuSO_4$ to afford the corresponding α-hydroxy ketone **7** and α,α′-dihydroxy ketone adducts in >90% yield without loss of enantioselectivity.[4]

On the basis of the absolute configuration, which is opposite to adducts **3** derived from Yamamoto's reaction,[19] we propose



Scheme 2. Asymmetric synthesis of (1*R*,2*R*)-*trans*-1,2-cyclohexanediol (**6**) and (2*R*)-hydroxycyclohexanone (**7**).

transition-state model **I** to account for the regio- and enantioselectivity of the α-oxidation reaction of unmodified substituted ketones (Scheme 3). Hence, (*S*)-proline forms an enamine with the ketone, which is attacked by the nitro-



I

Scheme 3. Transition-state models evoked to account for the regio- and enantioselectivity of the (*S*)-proline-catalyzed reaction.

sobenzene from its *se* face providing (2*R*)-α-aminoxylated ketones. This is in accordance with the transition states of previously reported proline-catalyzed Mannich and α-amination reactions, in which a *si*-facial attack occurs.[9,10,20] The proposed transition state **I** also explains how the unprecedented second attack of the electrophile could occur for the monoaminoxylated intermediate ($R^1 = ONHPh$).

In conclusion, we have developed the first direct enantioselective method that provides protected α-hydroxy ketones in $>99\%$ *ee*. The reactions were performed without tedious elaboration in wet solvents in the presence of air and are readily scaled up. In addition, reactions with α-unsubstituted cyclic ketones as donors in DMSO were remarkably selective, affording the corresponding C_2-symmetric α,α′-dihydroxy ketones with $>99\%$ *ee*. Further elaboration of this transformation and its synthetic application is being studied in our laboratory.[21]

Experimental Section

Typical experimental procedure (Table 1, entry 1): To a vial containing **2** (1 mmol) and a catalytic amount of (*S*)-proline (20 mol%) in $CHCl_3$ (4 mL) was added the ketone **1a** (1 mL, 10 equiv). After 2 h of vigorous stirring the reaction was quenched by the addition of aqueous NH_4Cl, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$, the solvent was removed under reduced pressure, and the crude product mixture was purified by silica gel column chromatography (EtOAc/pentane 1:8) to afford α-aminooxy ketone **3a** in 91% yield as slightly yellow solid. The enantiomeric excess of **3a** was $>99\%$ as determined by chiral-phase HPLC analysis. **3a**: ^{1}H NMR ($CDCl_3$): $\delta = 1.71$–1.79 (m, 4H), 2.00–2.02 (m, 2H), 2.34–2.48 (m, 2H), 4.35 (q, 1H, $J = 6.0$ Hz), 6.94 (t, 3H, $J = 8.1$ Hz), 7.25 (t, 2H, $J = 8.4$ Hz), 7.82 ppm (brs, 1H); ^{13}C NMR: $\delta = 23.7$, 27.2, 32.5, 40.8, 86.2, 114.3, 122.0, 128.8, 148.0, 209.9 ppm; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, $\lambda = 242$ nm): major isomer: $t_R = 30.31$ min; minor isomer: $t_R = 25.79$ min; $[\alpha]_D = +111.3$ ($c = 0.15$, $CHCl_3$); MALDI-TOF MS: 228.101; $C_{12}H_{15}NO_2$ (M+Na$^+$: calcd 228.100).

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[18] The α-oxy aniline adducts racemize and decompose upon storage in solution and at room temperature and should therefore be stored as solids at 4 °C or reduced to the more stable corresponding monoprotected diols.

[19] The optical rotation of **3a** obtained from the (*S*)-proline-catalyzed reaction was $[\alpha]_D = +111.3$ ($c = 0.15$, $CHCl_3$); reported rotation for (−)-**3a** is $[\alpha]_D = -53.0$ ($c = 0.62$, $CHCl_3$).[4] The optical rotation of **3c** was $[\alpha]_D = +57.7$ ($c = 2.1$, $CHCl_3$); the reported rotation for (−)-**3c** is $[\alpha]_D = -12.8$ ($c = 0.3$, $CHCl_3$).[4]

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