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Unfunctionalized, α-Epimerizable Nonracemic Ketones and Aldehydes Can Be Accessed by Crystallization-Induced Dynamic Resolution of Imines†

Janez Košmrlj,*,‡ Leland O. Weigel,*,§ David A. Evans,⊥ C. Wade Downey,⊥ and Jimmy Wu⊥

Chemical Process R&D, Lilly Research Laboratories, Indianapolis, Indiana 46285-4813, Faculty of Chemistry and Chemical Technology, University of Ljubljana, SI-1000 Ljubljana, Slovenia, and Department of Chemistry & Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Received December 12, 2002; E-mail: l.weigel@lilly.com; janez.kosmrlj@uni-lj.si

Over the past three decades, the requirements of the pharmaceutical industry for nonracemic chemical entities have been one of the major driving forces for the innovation of practical asymmetric synthetic methods. Although numerous advances based upon utilizing chiral pool materials, auxiliaries, asymmetric catalysis, crystallization-induced dynamic resolution (CIDR),[1] and biological transformations have been described, relatively few of these methods have been adapted to industrial applications.[2]

As part of our program on the development of practical resolution and deracemization processes,[2b] we required methodologies to manufacture large quantities of nonracemic, α-epimerizable, unfunctionalized ketones and aldehydes. Asymmetric alkylation sequences or resolutions are generally used to access nonracemic ketones or aldehydes (or their derivatives). Ultimately, many of these methods prove impractical for industrial development. A general method for the industrial production of nonfunctionalized, nonracemic ketones and aldehydes in high yield and ee has not yet been developed. Arguably, a simple deracemization process might prove most effective. There are CIDR methods of α-substituted carbonyl compounds that rely upon specialized functional groups (see Supporting Information).[3] Among these, Tsunoda's host−guest work demonstrates unique potential in the preparation of nonracemic ketones.[4]

We hypothesized that a truly practical dynamic resolution of unfunctionalized ketones or aldehydes might be achieved by a sequence of (a) formation of a crystalline imine derived from an epimerizable racemic ketone/aldehyde (*rac*-**1**) and a nonracemic amine X_c-NH_2 (**2**), (b) crystallization under conditions which allow CIDR of one diastereomer (*ent*-**3**), and (c) hydrolysis under acidic conditions with concurrent extractive separation of *ent*-**1** (organic phase) and the HA salt of **2** (aqueous phase, Scheme 1). Although conceptually straightforward, no such deracemization protocol has been published. Obviously, for success with ketones, one imine isomer among four must be selectively crystallized and hydrolyzed.

As goals for "industrial feasibility" we set critical success factors of (a) >90% yields, (b) >90% ee, (c) protocols as simple as a resolution, and (d) >95% recovery of the chiral amine **2** (X_c-NH_2). Toward these objectives, we undertook a parallel evaluation of the CIDR of imines derived from seven chiral amines [X_c-NH_2: (*R*)-α-methylbenzylamine, (*R*)-α-methyl-4-nitrobenzylamine, (*R*)-phenylglycine amide, (*S*)-1-(1-naphthyl)ethylamine, (*S*)-1-aminoindane, *trans*-(1*R*,2*R*)-1-aminoindan-2-ol, and *trans*-(1*R*,2*R*)-6-nitro-1-aminoindan-2-ol (*R*,*R*-**2**)[5a]] with *d*,*l*-2-methylcyclohexanone (*rac*-**1a**) and *d*,*l*-2-ethylhexanal (*rac*-**1b**) in various solvents[5b] and in the presence of several common catalysts.[5c] The ketimines formed (in solution) were *E*/*Z* mixes and usually 1:1 dr on the basis of the epimerizable stereogenic center (e.g., four isomers observable by NMR analysis with imines of 2-methylcyclohexane). The aldimines were usually >95% *E* but again close to 1:1 dr. Attempted crystallization of all of the imines under a variety of conditions led to oils or waxes, except in the case of (*R*,*R*)-**2**. Both imines **3a** and **3b** (derived from **1a** and **1b** with (*R*,*R*)-**2**, Table 1) formed crystalline solids. Ketimine **3a** formed a 3:1 solution mixture of *E*:*Z* imine isomers (Scheme 2) with a dr of 1:1. The feasibility of

Scheme 1. Generalized Scheme for Deracemization of Ketones/Aldehydes (**1**) via CIDR of Imines (**3**)

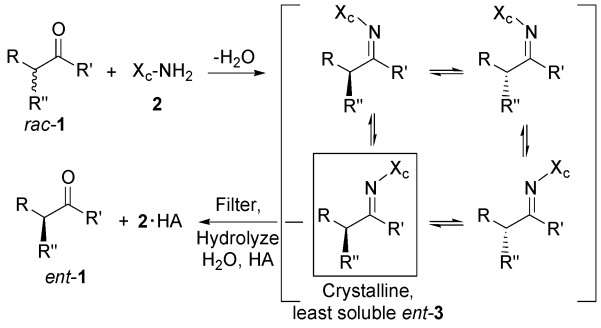
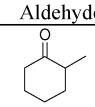
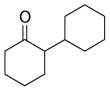


Table 1. Synthesis and CIDR of **3** and Its Hydrolysis to *ent*-**1**[a]

Ketone/ Aldehyde	Imine **3** yield,[b]	CIDR of **3** Solvent, yield, de[c]	Hydrolysis of **3** *ent*-**1**, yield,[d] ee,[e]
 **1a**	**3a** 97	MeOH, 100, 92	(*R*)-**1a**, 97, 92[f] 94, 90[g]
 **1b**	**3b** 100	MeOH, 100, 99	(*R*)-**1b**, 94, 98[f] 98, 90[h] –[i] 50[j] –[i] 20[k]
 **1c**	**3c** 100	MeOH, 70, 99	(*R*)-**1c**, 94, 98[f] –[i] 10[g]
 **1d**	**3d** 98	Ether, 74, 98	**1d**,[l] –[i] 98[f]
 **1e**	**3e** 91	hexane/THF, 100, 76	**1e**,[l] –[i] 76[g]

[a] All imines derived from (*R*,*R*)-**2**. See ref 6 and Supporting Information. [b] Isolated yields based on input (*R*,*R*)-**2**. [c] Diastereomeric excesses (%) by ^{1}H NMR. [d] Quantitative GLC analysis. [e] Enantiomeric excess by chiral GLC. [f] Hexane/aqueous $CuCl_2$ hydrolysis. [g] Hexane/NaOAc−HOAc buffer (pH 4.1) hydrolysis. [h] Hexane/NaOAc−HOAc buffer (pH 3.8) hydrolysis. [i] Not determined. [j] Oxalic acid. [k] HCl. [l] Absolute configuration not yet determined.

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‡ University of Ljubljana.
§ Lilly Research Laboratories.
⊥ Harvard University.

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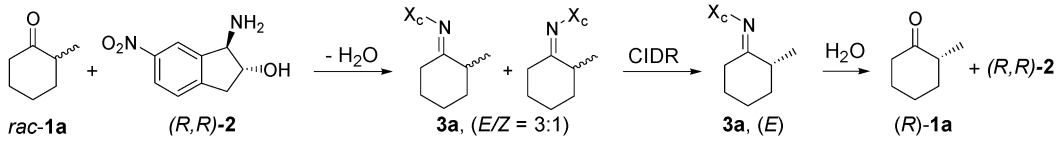
Scheme 2. Deracemization of *rac*-**1a**



CIDR was demonstrated in our first experiment when a THF−hexane solution of ketimine **3a** was allowed to crystallize (50 to 25 °C, 24 h). Assay of the **3a** (90% isolated yield) indicated approximately 3:1 dr (NMR in DMSO-d_6). The dr slowly eroded during NMR analysis, making accurate evaluations difficult. Therefore, we used chiral GLC of the ketone or aldehyde after imine hydrolysis for accurate determinations. The enantiomeric excesses of ketones/aldehydes represented herein are a result of the two-stage sequence of CIDR and hydrolysis.

In the CIDR of **3a**, best results were obtained when the unpurified solid imine was stirred as a solid−liquid mixture at 23 °C (prolonged heating yielded minor decomposition which complicated the crystallization). Polar solvents (e.g., methanol, ethanol, 2-propanol, and acetonitrile) proved more effective than less polar solvents (e.g., hexane, ether, and THF). Equilibration of **3a** in methanol and hydrolysis (vide infra) afforded (*R*)-**1a** with an ee of 90−92% in 91−94% overall yield from *rac*-**1a** (Table 1).

Of the numerous published methods for Schiff base hydrolysis,[7] two methods worked best (Table 1). Biphasic hydrolysis of **3a** with hexane/acetic acid−sodium acetate buffer,[8] yielded (*R*)-**1a** in 94% yield and 90% ee. Under these conditions, (*R*)-**1a** was extracted into the hexane phase as hydrolysis occurred and the acetate salt of (*R*,*R*)-**2** could be recovered from the water phase by merely adjusting to pH 10 and filtering (95% average yield of (*R*,*R*)-**2**, suitable for reuse). Hydrolytic conditions with hexane/aqueous $CuCl_2$ (initially introduced for the hydrolysis of hydrazones)[9] afforded (*R*)-**1a** in 97% yield and 92% ee (Table 1).

Our deracemization protocol for *d*,*l*-ethylhexanal (*rac*-**1b**) proved to be amazingly simple and provided enzyme-like selectivity. Aldimine **3b** was prepared by treating *rac*-**1b** with (*R*,*R*)-**2** (1:1 diastereomers, approximately 100% yield based on (*R*,*R*)-**2**).[6] A simple "one-pot" procedure of imine formation and stirring/concentration afforded pure **3b** (dr 99:1). Hydrolysis with aqueous $CuCl_2$ afforded (*R*)-**1b** (98% ee, 94% overall yield) whereas hydrolysis with NaOAc−HOAc (industrially advantageous) gave a small amount of racemization (98% overall yield by quantitative GLC, 90% ee). The yield of **1b** was corroborated by subsequent formation of the 2,4-DNP derivative.[6] The critical nature of acid/pH is demonstrated by the hydrolysis of **3b** with four different acids (Table 1).

The CIDR with three additional ketones (**1c**, **1d**, **1e**, Table 1) suggests that the process is general. Deracemization of *rac*-**1c** is difficult due to lability of the stereogenic center,[10] and few reliable methods exist for the preparation of *ent*-**1c**. The unoptimized CIDR process afforded **3c** (70% yield, dr = 99%) and the ketone **1c** in 98% ee (aqueous $CuCl_2$ hydrolysis). Without optimization, imines **3d** and **3e** underwent CIDR to afford substantial enrichment (Table 1).

To better understand the origin of this highly effective CIDR, we analyzed **3b** by single-crystal X-ray diffraction. Elucidation of the crystal structure of **3b** revealed an extremely ordered state with π-stacking of the (*R*,*R*)-**2** and, in a nearly orthogonal fashion, a hydrogen-bonding sheet[11] in which the hydroxyl proton of (*R*,*R*)-**2** is hydrogen bonded to an imine nitrogen (see ORTEP and crystal packing data in the Supporting Information). This very rigid array leads to a high degree of stereogenic discrimination during the dynamic crystallization (e.g., ethyl vs butyl in **1b**).

In summary, we have demonstrated unoptimized CIDR of five ketones/aldehydes with (*R*,*R*)-**2**. Our results with **1b** demonstrate enzyme-like selectivity and industrial feasibility. Future endeavors will focus on developing more general hydrolysis conditions as well as superior chiral auxiliaries.

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Supporting Information Available: References on CIDR, experimental procedures, ORTEP plot of **3b** (PDF) and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) (a) Gruber et al. WO Patent 9951236, October 14, 1999. Also obtained by resolution with mandelic acid, unpublished: Patterson, L.; Hansen, M.; Kolis, S.; Ditsworth, T. Eli Lilly and Co., 2002. (b) THF, methanol, ethanol, IPA, diglyme, hexane, triethyl orthoformate, ether, acetonitrile. (c) HOAc, 4 Å sieves, TFA, silica gel, alumina, TsOH.
(6) Example synthesis of (*R*)-**1b** (all operations at 23 °C): A mixture of *rac*-**1b** (7.05 g, 96% purity, 53 mmol) and (*R*,*R*)-**2** (50 mmol) in THF (0.15 L) was stirred for 30 min. The volatile compounds were evaporated in a stream of nitrogen (5 mL/h) to give **3b** (dr 3:1). The enriched **3b** was stirred in methanol (0.1 L, 6 h) and evaporated (nitrogen stream) to afford **3b** (dr 96:4). Repeating the above sequence twice (70 mL and 50 mL of MeOH) resulted in **3b** (dr 99:1), 100% yield based on (*R*,*R*)-**2**). The aldimine **3b** (20 mmol) was allowed to stir with hexane (0.24 L), diethyl ether (0.1 L), and sodium acetate/acetic acid buffer (pH 3.8, 0.14 L; under nitrogen, 1 h). The layers were separated and the aqueous layer was extracted with hexane (3 × 50 mL). The standardized solution was analyzed by quantitative GLC (98% yield (*R*)-**1b** based on input (*R*,*R*)-**2**; reaction with 2,4-dinitrophenylhydrazine (2,4-DNP) yielded 93% of the hydrazone), and by chiral GLC (90% ee (*R*)-**1b**).
(7) For recent review, see: Enders, D.; Wortmann, L.; Peters, R. *Acc. Chem. Res.* **2000**, *33*, 157−169.
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