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Base-Catalyzed Isomerization of 2-Isoxazolines Enables a Two-Step Enantioselective Synthesis of β-Hydroxynitriles from Enals

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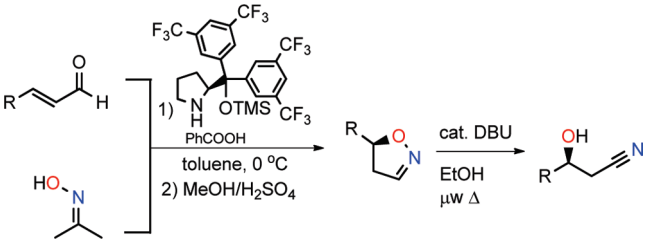
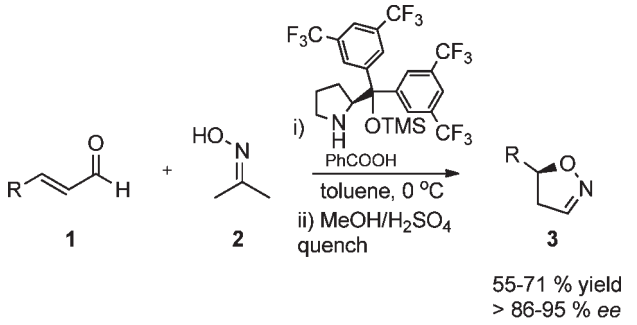


The asymmetric synthesis of β-hydroxynitriles remains a challenge in organic synthesis. Herein we report a convenient synthesis of β-hydroxynitriles from enantiomerically enriched 3-unsubstituted 2-isoxazolines via a base-catalyzed ring-opening reaction that takes place without loss of enantiopurity. In combination with organocatalytic enantioselective synthesis of 3-unsubstituted 2-isoxazolines, the ring-opening enables a short 2-step synthesis of β-hydroxynitriles from α,β-unsaturated aldehydes in high enantiomeric purity.

β-Hydroxynitriles are valuable synthetic intermediates in chemical synthesis, allowing access to, e.g., β-hydroxy acids and β-hydroxycarbonyl compounds.[1] The synthesis of these compounds in an enantioselective manner is still challenging, and methods for the direct catalytic asymmetric synthesis of β-hydroxynitriles are scarce. The currently available methods for the synthesis of β-hydroxynitriles include the asymmetric nitrile aldol reaction,[2,3] the asymmetric hydroboration of α,β-unsaturated nitriles,[4] the nucleophilic opening of terminal epoxides with cyanide,[5] the enzymatic resolution of racemic nitriles[6] or the corresponding cyanoacetates,[7] and the asymmetric reduction of α-cyanoacetophenones.[8] However, the synthesis of β-hydroxynitriles bearing diverse alkylic substituents at the β-position with high enantioselectivity is still challenging, and the best enantioselectivities are typically obtained by resolution techniques.[6]

SCHEME 1. Synthesis of Enantiomerically Enriched 2-Isoxazolines from Enals



We have recently disclosed two methods for the preparation of 3-unsubstituted 2-isoxazolines in both racemic and enantioselective manner from α,β-unsaturated aldehydes and oximes (Scheme 1).[9] These methods can be used to access a diverse range of 2-isoxazolines bearing alkyl or substituted alkyl substituents at the 5-position. In principle, these isoxazolines could be converted to β-hydroxynitriles via a base-catalyzed isomerization reaction, first documented by Huisgen and Christl[10] in 1967. Although a number of 2-isoxazoline to β-hydroxynitrile rearrangements have been reported, these have been limited to isolated examples of special interest, partly due to limitations in the synthesis of the parent heterocycles.[11] In these examples, the isomerization has been effected by

(1) For selected examples of the use of chiral β-hydroxynitriles in natural product synthesis, see: (a) Hijikuro, I.; Doi, T.; Takahashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 3716–3722. (b) Gogoi, S.; Barua, N. C.; Kalita, B. *Tetrahedron Lett.* **2004**, *45*, 5577–5579. (c) Wang, F.; Yue, J. *Eur. J. Org. Chem.* **2005**, 2575–2579. (d) Pospišil, J.; Markó, I. E. *J. Am. Chem. Soc.* **2007**, *129*, 3516–3517.

(2) (a) Soai, K.; Mukaiyama, T. *Bull. Chim. Soc. Jpn.* **1979**, *52*, 3371–3376. (b) Soai, K.; Hirose, Y.; Sakata, S. *Tetrahedron: Asymmetry* **1992**, *3*, 677–680. (c) Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2021–2027.

(3) For a truly catalytic asymmetric nitrile aldol reaction, see: Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757–3760.

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(6) For examples, see: (a) Kamal, A.; Ramesh Khanna, G. B.; Ramu, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2039–2051. (b) Kamal, A.; Ramesh Khanna, G. B.; Krishnaji, T.; Tekumalla, V.; Ramu, R. *Tetrahedron: Asymmetry* **2005**, *16*, 1485–1494. (c) Fransson, A.-B. L.; Boren, L.; Pamies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2005**, *70*, 2582–2587. (d) Kamal, A.; Ramesh Khanna, G. B.; Krishnaji, T.; Ramu, R. *Tetrahedron: Asymmetry* **2006**, *17*, 1281–1289.

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(10) (a) Huisgen, R.; Christl, M. *Angew. Chem.* **1967**, *79*, 471. (b) Huisgen, R.; Christl, M. *Chem. Ber.* **1973**, *106*, 3291–3311.

(11) The synthesis of 3-unsubstituted 2-isoxazolines from alkenes and fulminic acid or silyl nitronate has been limited to alkenes containing a stabilizing substituent.

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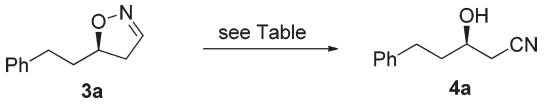
TABLE 1. Comparison of Conditions for the Ring-Opening of 2-Isoxazoline 3a[a]



entry	solvent	base (mol %)	time	temp (°C)	[X][b]	ee (**3a**)/ee (**4a**)
1	Et_3N	solvent	3 h	rt	0	n/d
2	Et_3N	solvent	3 h	reflux	0	n/d
3	THF	KO*t*Bu (2)	10 min	rt	100/97[c]	80/**70**
4	MeOH	NaOMe (2)	45 min	rt	100/88[c]	80/79
5	THF	KHMDS (130)[d]	60 min	−15	100/58−91[c]	91/91
6	toluene	Et_3N (100)	3 h	reflux	0	n/d
7	MeCN	Et_3N (100)	3 h	reflux	< 10	n/d
8	EtOH	Et_3N (100)	3 h	rt	0	n/d
9	EtOH	Et_3N (100)	3 h	reflux	40	n/d
10	EtOH	DBU (100)	3 h	rt	90	n/d
11	EtOH	DBU (100)	30 min	reflux	100	n/d
12	EtOH	DBU (25)	30 min	reflux	100	94/94[e]
13	EtOH	DBU (25)	10 min	85 /μw	100/94[c]	94/94

[a]Conditions: 0.1 mmol **3a**, 0.5 mL solvent. [b]Conversion (X) of **3a** was determined by ^{1}H NMR. *p*-Bromoanisole was used as the internal standard. [c]Isolated yield. [d]The use of catalytic amounts of KHMDS gave inferior results. [e]Determined in conjunction with the telescoped experiment (see Scheme 2).

using triethylamine as solvent[10,12,13] or as a catalytic[14] or stoichiometric[15] reagent in methanol, toluene,[16] and acetonitrile.[17] The use of sodium methoxide in methanol[18] has also been reported in a single case. However, the general applicability of these examples has not been demonstrated, since the reactions have typically been carried out with either strained[13,16] or electronically activated[10,12,14,15,17,18] substrates, and the issues of enantiomeric purity have not been addressed.

Herein we report a simple and effective catalytic protocol that allows the rapid synthesis of enantiomerically enriched β-hydroxynitriles from chiral 2-isoxazolines in excellent yields and with full conservation of enantiomeric purity.

We initiated our study with the substrate **3a**, containing an alkyl chain at the 5-position. Initial attempts to generate the β-hydroxynitrile **4a** with triethylamine as the base and the solvent were met with complete failure (Table 1, entries 1 and 2). Consequently, several other base/solvent combinations were screened (Table 1).

The base screen indicated that previously disclosed methods were not directly applicable to nonactivated substrates such as **3a**. The suppressed reactivity of alkyl substrates was reported also by Huisgen and Christl.[10b] While strong anionic bases such as KHMDS, KO*t*-Bu, or NaOMe (entries 3−5) led to rapid reactions even at cold temperatures, the chemical yields of these processes were often inconsistent and seemed to be dependent on the quality of the base. We were also concerned that the use of highly nucleophilic methoxide base might be too restrictive in terms of functional group diversity in the substrates. Furthermore, an even more worrying result was obtained with KO*t*-Bu in THF, where a partial loss of enantiomeric purity was observed (Table 1, entry 3). This result was likely caused by the reversible retro-nitrile aldol reaction.

Turning to weaker nonanionic nitrogen bases, we found that Et_3N was only effective when an alcoholic solvent was used (entries 6−9) and the reaction was heated to reflux, but even then the reaction was quite sluggish.[19] The use of a slightly more basic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) dramatically improved the rates. Under refluxing conditions, full conversion of the starting material to the product was observed in 30 min, even when a catalytic amount of DBU was used.[20] The reaction could also be conducted very conveniently in a microwave reactor: in a pressurized microwave vial with 50 W heating power, full conversion was obtained within 10 min. **4a** was isolated in excellent yield and unchanged enantioselectivity (94% yield, 94% ee).

The scope of the optimized protocol was then screened with a structurally diverse set of enantioenriched 2-isoxazolines, readily accessible from α,β-unsaturated aldehydes and oximes[9c] (Table 2). A range of substrates bearing different substituents in the 5-position of the isoxazoline could readily be converted into the corresponding β-hydroxynitriles, including a 5,5-disubstituted isoxazoline **3g** bearing a tertiary center (entry 7). Different protecting groups (silyl, benzyl, Cbz) were found to readily withstand the reaction conditions (entries 3, 5, and 6), and even the unsaturated ester side chain present in **3h** afforded a good yield of the product; however, in this case, the ring-opening reaction (entry 8) had to be conducted at room temperature with methanol as the solvent to avoid transesterification and to suppress the internal conjugate addition of **4h** to form tetrahydropyrans.[21]

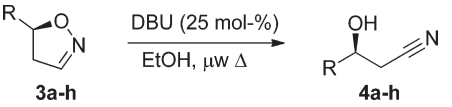
Finally, we conducted the synthesis of **4a** as a direct two-step protocol without purification of the 2-isoxazoline product. This telescoped protocol afforded the product in 73% overall yield and 94% enantiomeric excess (Scheme 2).

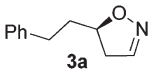
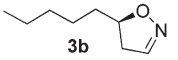
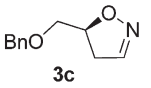
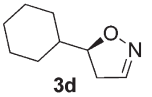
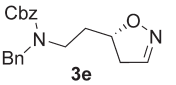
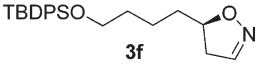
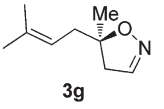
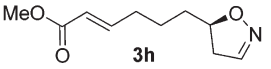
As a conclusion, we have demonstrated that under optimized conditions, base-catalyzed isomerization of 3-unsubstituted

(12) Das, N. B.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2247–2253.
(13) Brand, U.; Hünig, S. *Liebigs Ann.* **1996**, 585–592.
(14) Galley, G.; Jones, P. G.; Pätzel, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2073–2082.
(15) Ogamino, T.; Nishiyama, S. *Tetrahedron* **2003**, *59*, 9419–9423.
(16) Irngartinger, H.; Weber, A. *Tetrahedron Lett.* **1997**, *38*, 2075–2076.
(17) Lukevics, E.; Dirnens, V.; Kemme, A.; Popelis, J. *J. Organomet. Chem.* **1996**, *521*, 235–244.
(18) (a) Andersen, S.; Das, N. B.; Jørgensen, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell, K. B. G. *Acta. Chem. Scand. B* **1982**, *36*, 1–14. (b) Yashiro, A.; Nishida, Y.; Kobayashi, K.; Ohno, M. *Synlett* **2000**, 361–362.

(19) Other solvents reported in the literature, such as toluene and acetonitrile, did not work at all with Et_3N as the base.
(20) Interestingly, DBU was reported to be ineffective in the ring opening of a [60]fullereno[1,2-*d*]isoxazole. See ref 16.
(21) (a) The formation of the side products could not be completely suppressed, and this is the likely reason for the slightly lower yield obtained with **2h** compared to other substrates. (b) In addition to MeOH and EtOH as the solvents, the reaction of **1h** in less nucleophilic solvent, *i*-PrOH, was also attempted. However, only a very slow reaction was observed, even upon heating.

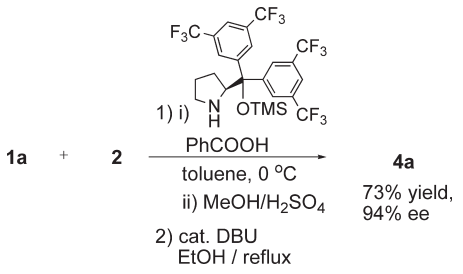
TABLE 2. Synthesis of Enantioenriched β-Hydroxynitriles from 2-Isoxazolines[a]



Entry[a]	Substrate	ee (%) of 3	Microwave conditions	Time (min)	Yield (%)	ee (%) of 4
1	 3a	94	50 W / 85 °C	15 min	94	94
2	 3b	94	50W / 94 °C	10 min	88	92
3	 3c	95	50 W / 85 °C	10 min	95	95
4	 3d	91	50 W / 85 °C	15 min	91	91
5	 3e	92	50 W / 102 °C	15 min	91	93
6	 3f	94	50W / 101 °C	15 min	96	93
7	 3g	69	50 W / 100 °C	20 min	89	69
8[b]	 3h	94	20 °C (no microwave)	4.5 h	75	93

[a]Conditions: (a) 1 mmol of 2-isoxazoline, 0.25 mmol of DBU, 4 mL of EtOH; (b) 1 mmol of 2-isoxazoline, 0.25 mmol of DBU, 4 mL of MeOH.

SCHEME 2. A Telescoped Two-Step Protocol for the Synthesis of β-Hydroxynitrile 4a



2-isoxazolines can be used efficiently in the asymmetric synthesis of β-hydroxynitriles. The ring-opening proceeds under fairly mild conditions with catalytic amounts of amine base (DBU) in methanol or ethanol. Heating the reaction results in fast reaction rates, but for sensitive substrates, the reaction can also be conducted at rt. Importantly, the enantiomeric purity of the 2-isoxazoline is fully conserved in the process, enabling a simple two-step synthesis of β-hydroxynitriles directly from the α,β-unsaturated aldehydes, even without purification of the intermediates. The implementation of the full protocol from α,β-unsaturated aldehydes to β-hydroxynitriles on supported catalysts has been initiated.

Experimental Section

General Procedure for the Ring-Opening of Isoxazolines under Microwave Conditions: Synthesis of (*R*)-3-Hydroxy-5-phenylpentanenitrile 4a. To a solution of 2-isoxazoline **3a** (173 mg, 1.00 mmol, 100 mol %) in EtOH (4 mL) in a microwave glass vessel was added DBU (35 μL, 0.25 mmol, 25 mol %). The resulting mixture was heated in a microwave reactor with constant power (50 W, 10 mL sealed vessel) at 83 °C, using air cooling to adjust the temperature. After the reaction was complete (indicated by TLC), the solution was concentrated to a volume of ca. 1 mL with a rotary evaporator and then diluted with EtOAc (20 mL). The resulting solution was washed with 1 M HCl (5 mL) and the aqueous layer was back-extracted with EtOAc (5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (27% EtOAc/hexane) afforded the product **4a** as a pale yellow solid (164 mg, 95%, 94% ee by HPLC). Mp 44−46 °C (lit.[22] mp 42−43 °C); R_f 0.33 (50% EtOAc in hexane); $[\alpha]_D$ +13.5 (*c* 1.0, CH_2Cl_2, 94% ee) {lit.[22] $[\alpha]_D$ +20 (*c* 1.6, $CHCl_3$, >99% ee)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.27 (m, 2H), 7.25−7.18 (m, 3H), 3.94 (qn, 1H, J = 5.8 Hz), 2.82 (ddd, 1H, J_1 = 5.9 Hz, J_2 = 8.5 Hz, J_3 = 14.0 Hz), 2.71 (td, 1H, J_1 = 8.0 Hz, J_2 = 14.0 Hz), 2.55 (dd, 1H, J_1 = 4.8 Hz, J_2 = 16.7 Hz), 2.50 (dd, 1H, J_1 = 6.4 Hz, J_2 = 16.7 Hz), 2.35 (br s, 1H), 2.0−1.84 (m, 2H). The analytical data correspond to those reported in the literature.[22] The enantiomeric purity was determined by HPLC analysis with a Daicel Chiralcel OD column (25 cm) along with precolumn (5 cm). Eluent: 10% 2-propanol in hexane. Flow rate: 0.7 mL/min. λ = 254 nm. Major isomer: t_r = 38.3 min. Minor isomer: t_r 31.6 min.

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(22) Wang, D.-F.; Yue, J.-M. *Eur. J. Org. Chem.* **2005**, 2575–2579.

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Supporting Information Available: General experimental methods, full experimental details, characterization data, copies of NMR spectra, microwave heating profiles, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.