Regioselective Bioamination

DOI: 10.1002/anie.201202375

Regio- and Stereoselective Monoamination of Diketones without Protecting Groups**

*Robert C. Simon, Barbara Grischek, Ferdinand Zepeck, Andreas Steinreiber, Ferdinand Belaj, and Wolfgang Kroutil**

Regioselective transformations are highly desirable in organic synthesis, since they allow for the differentiation between two or more (chemically identical) reactive centers,[1] which is otherwise only possible by employing sophisticated and laborious protection strategies.[2] However, protecting-group-free strategies are superior and have received outstanding merits for their successes.[3,4] Although the regioselective amination of, for example, alkanes,[5] allylic systems,[6] or indoles,[7] has been recently described, the regioselective asymmetric bioamination of diketones has not yet been reported, to the best of our knowledge. For example, diketones, such as 1,5-diketo compounds, may serve as possible precursors for a chiral piperidine scaffold.[8] Consequently, we chose 2,6-diketones **1** as model substrates to investigate the possible asymmetric regioselective amination employing ω-transaminases (ω-TAs; Scheme 1).[9,10]

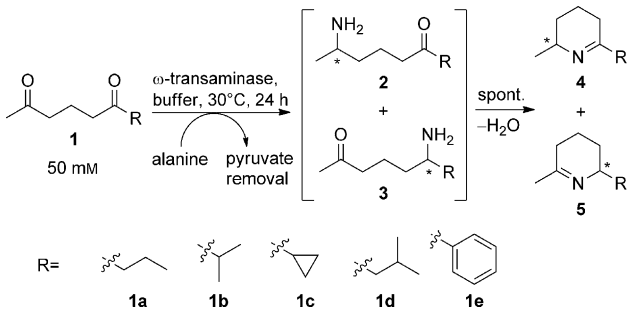
Various (*S*)- and (*R*)-stereoselective ω-transaminases were tested initially for the transformation of diketone **1a** at a substrate concentration of 50 mM (Table 1). Five ω-TAs (*Chromobacterium violaceum*,[10i,11] *Bacillus megaterium*,[10i,12] (*R*)-*Arthrobacter*,[10b] *Aspergillus terreus*, and *Hyphomonas neptunium*[10b,h]) out of six showed perfect regioselectivity for the differentiation between the two keto groups. Hence, the amination occurred exclusively at the sterically less demanding ω-1 ketone moiety, leading to the amino ketone **2a**, while the ω-3 position remained untouched. The intermediate amino ketone **2a** spontaneously cyclized, finally giving Δ1-piperideine **4a**. Only the ω-TA from *Vibrio fluvialis*[9h,13] (entry 3) showed diminished regioselectivity, since regioisomer **5a** was formed in minor quantities (5–7%) along with regioisomer **4a** at high conversion. Notably, the corresponding diamine was never detected in any experiment.

Using alanine as amine donor led to the formation of pyruvate as a by-product, which was removed/recycled to alanine through the use of an alanine dehydrogenase (AlaDH) system. In all cases, perfect conversions were achieved for this system. When removing pyruvate by reduction to lactate through the use of a lactate dehydrogenase (LDH) system, the conversions varied from 56–98%. The

Table 1: Asymmetric reductive amination of diketone **1a**.[a]

		AlaDH system				LDH system			
Entry	ω-TA	conv [%]	**4a** [%]	*ee* **4a** [%]	**5a** [%]	conv [%]	**4a** [%]	*ee* **4a** [%]	**5a** [%]
1	*C. violaceum*	>99	>99	>99 (*S*)	<0.1	93	93	>99 (*S*)	<0.1
2	*B. megaterium*	>99	83[b]	>99 (*S*)	<0.1	98	98	>99 (*S*)	<0.1
3	*V. fluvialis*	>99	93	>99 (*S*)	7	98	92	>99 (*S*)	6
4	(*R*)-*Arthrobacter*	>99	87[b]	>99 (*R*)	<0.1	63	63	>99 (*R*)	<0.1
5	*A. terreus*	>99	>99	>99 (*R*)	<0.1	56	56	>99 (*R*)	<0.1
6	*H. neptunium*	>99	89[b]	>99 (*R*)	<0.1	78	78	>99 (*R*)	<0.1

[a] Conversions/compositions and *ee* values were determined by GC-FID analysis. Reaction conditions: diketone **1a** (50 mM), lyophilized *E. coli* cells containing the overexpressed ω-TA (20 mg), PLP (1 mM), NAD^+ (1 mM), D- or L-alanine (5 equiv), 24 h, 30°C, AlaDH system (12 U AlaDH, 11 U FDH, 150 mM ammonium formate) or LDH system (90 U LDH, 15 U GDH, 5 equiv D- or L-alanine, 150 mM glucose). [b] An unidentified side product was detected by GC analysis; therefore, the percentage of **4a** and **4b** does not sum up to the percentage of the conversion.



Scheme 1. Regioselective amination of various 1,5-diketones.

[*] Dr. R. C. Simon
ACIB GmbH
Heinrichstrasse 28, 8010 Graz (Austria)
Dr. F. Zepeck, Dr. A. Steinreiber
Sandoz GmbH, Biocatalysis Lab
Biochemiestrasse 10, 6250 Kundl/Tirol (Austria)
Prof. Dr. F. Belaj
University of Graz
Schubertstrasse 1, 8010 Graz (Austria)
B. Grischek, Prof. Dr. W. Kroutil
University of Graz, Institute of Chemistry
Organic and Bioorganic Chemistry
Heinrichstrasse 28, 8010 Graz (Austria)
E-mail: wolfgang.kroutil@uni-graz.at

[**] This work was supported by the Austrian BMWFJ, BMVIT, SFG, Standortagentur Tirol, and ZIT through the Austrian FFG-COMET Funding Program. Financial support by NAWI Graz is also acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201202375.

removal of the pyruvate by-product formed was required to shift the reaction to the product side.

Depending on the choice of ω-TA, both (*S*)-**4a** (Table 1, entries 1–3) and (*R*)-**4a** (Table 1, entries 4–6) were accessible in an optically pure form. Thus, all enzymes tested displayed perfect stereoselectivity for the exclusive formation of a single enantiomer (> 99 % *ee*).

Testing other diketones, **1b–e**, demonstrated the general applicability of this approach to access chiral Δ1-piperideines **4b–e** (Table 2). For example, substrate **1b** was regio- and stereoselectively aminated, leading to both the *R* and *S* enantiomers in high conversions (> 90 %) and enantiomeric excesses of > 99 % (Table 2, entries 1–5). Notably, no regioisomeric imines **5b–e** could be detected for any of the substrates **1b–e** tested, thus the imines **4b–e** were exclusively formed.

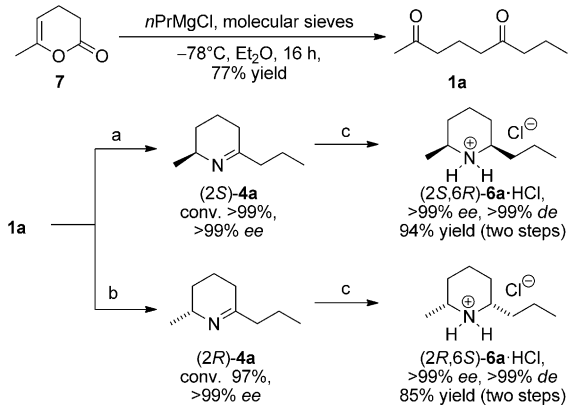
Table 2: Regioselective asymmetric reductive amination of diketones **1b–e** employing various ω-transaminases.[a]

Entry	Substrate	ω-TA	Conv [%]	**4** [%]	*ee* **4** [%]	**5** [%]
1	**1b**	*C. violaceum*	93	93	> 99 (*S*)	< 0.1
2	**1b**	*V. fluvialis*	90	90	> 99 (*S*)	< 0.1
3	**1b**	(*R*)-*Arthrobacter*	94	94	> 99 (*R*)	< 0.1
4	**1b**	*A. terreus*	93	93	> 99 (*R*)	< 0.1
5	**1b**	*H. neptunium*	94	94	> 99 (*R*)	< 0.1
6	**1c**	*C. violaceum*	> 99	> 99	> 99 (*S*)	< 0.1
7	**1c**	*V. fluvialis*	> 99	> 99	> 99 (*S*)	< 0.1
8	**1c**	(*R*)-*Arthrobacter*	> 99	> 99	> 99 (*R*)	< 0.1
9	**1c**	*H. neptunium*	> 99	> 99	> 99 (*R*)	< 0.1
10	**1d**	*C. violaceum*	> 99	> 99	> 99 (*S*)	< 0.1
11	**1d**	*B. megaterium*	> 99	> 99	> 99 (*S*)	< 0.1
12	**1d**	*V. fluvialis*	> 99	> 99	98 (*S*)	< 0.1
13	**1d**	(*R*)-*Arthrobacter*	> 99	> 99	> 99 (*R*)	< 0.1
14	**1d**	*A. terreus*	> 99	> 99	> 99 (*R*)	< 0.1
15	**1d**	*H. neptunium*	> 99	> 99	> 99 (*R*)	< 0.1
16	**1e**[b]	*C. violaceum*	> 99	> 99	92 (*S*)	< 0.1
17	**1e**[b]	*B. megaterium*	27	27	> 99 (*S*)	< 0.1
18	**1e**[b]	(*R*)-*Arthrobacter*	> 99	> 99	> 99 (*R*)	< 0.1
19	**1e**[b]	*H. neptunium*	86	86	> 99 (*R*)	< 0.1

[a] Conversions/compositions and *ee* values were determined by GC-FID analysis. Reaction conditions: diketone **1b–e** (50 mM), lyophilized *E. coli* cells containing the overexpressed ω-TA (20 mg), 1 mM PLP, 1 mM NAD^+, 5 equiv D- or L-alanine, 24 h, 30 °C, AlaDH system (12 U AlaDH, 11 U FDH, 150 mM ammonium formate). [b] 5 vol % 1,2-dimethoxyethane (DME) added.

The preparative synthetic potential of this method was demonstrated in the synthesis of the natural alkaloid (+)-dihydropinidine ((2*S*,6*R*)-**6a**), a potential antifeedant against the pine weevil *Hylobius abietis*,[14] as well as its enantiomer (2*R*,6*S*)-**6a**. The required diketone **1a** was obtained in one step, starting from commercially available diyhdropyrane-2-one **7** (Scheme 2). Diketone **1a** (78 mg, 0.5 mmol) was then successfully regioselectively aminated through the use of the ω-TA from *C. violaceum* to access (*S*)-**4a**, and the (*R*)-selective ω-TA originating from *Arthrobacter* sp. to obtain (*R*)-**4a**, as described above. Both enantiomers were obtained in optically pure form (> 99 % *ee*) and with conversions of > 99 % for (2*S*)-**4a** and 97 % for (2*R*)-**4a**. The isomers of **4a** were then readily converted by diastereoselective hydrogenation (H_2, Pd/C) to establish the second chiral center, affording piperidines **6a** with perfect diastereoselectivity (> 99 % *de*; Figure 1). The natural product (2*S*,6*R*)-**6a**, and its enantiomer, (2*R*,6*S*)-**6**, were obtained in 94 % and 85 % yield, respectively, over two steps. Thus, starting from pyranone **7**, optically pure (+)-dihydropinidine was obtained in just three steps with a respectable overall yield of 72 %. Piperidine (2*S*,6*R*)-**6a** has already been the object of numerous synthetic efforts, which have resulted in a variety of asymmetric syntheses based on, for example, chiral auxiliaries and chiral precursors.[15] Although some syntheses are highly sophisticated, long reaction sequences (up to 14 steps),[15f,h] the use of protecting groups or stoichiometric amount of auxiliaries[15c,g] hampered their overall efficiency. Thus, the chemoenzymatic[16] synthesis of 2,6-disubsituted chiral piperidines based on the regioselective amination of diketones presented herein represents the shortest route by far, with an excellent overall yield.

In a similar fashion, diketones **1b–e** were also regioselectively aminated on a preparative scale (0.5 mmol), followed by diastereoselective hydrogenation. In this way, optically pure *syn*-2-methyl-6-substituted piperidines



Scheme 2. Chemoenzymatic total synthesis of (+)-dihydropinidine ((2*S*,6*R*)-**6a**) and its enantiomer. Reagents and conditions: a) Diketone **1a** (78 mg, 0.5 mmol, 50 mM), ω-TA from *C. violaceum*, PLP (1 mM), NAD^+ (1 mM), L-alanine (10 equiv), ammonium formate (150 mM), 11 U FDH, 12 U AlaDH; 26 h, 30 °C, 120 rpm; b) Same as for (a), but with (*R*)-ω-TA from *Arthrobacter* sp. and 2 h; c) Pd/C, H_2, 4 h, 22 °C.

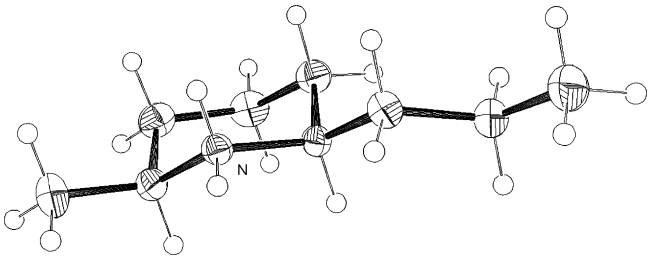
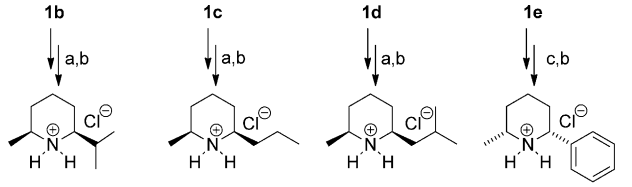


Figure 1. Stereoscopic ORTEP plot of the HCl salt of (+)-dihydropinidine ((2*S*,6*R*)-**6a**·HCl). Ellipsoids set at 50 % probability. The chlorine atom was omitted for clarity.



(2*S*,6*S*)-**6b**·HCl >99% *ee*, >99% *de* 90% yield (2 steps) | (2*S*,6*S*)-**6a**·HCl >99% *ee*, >99% *de* 65% yield (2 steps) | (2*S*,6*S*)-**6d**·HCl >99% *ee*, >99% *de* 79% yield (2 steps) | (2*R*,6*R*)-**6e**·HCl >99% *ee*, >99% *de* 94% yield (2 steps)

Scheme 3. Optically pure 2,6-disubstituted piperidines synthesized. Reagents and conditions: a) **1b–d** (0.5 mmol), ω-TA from *C. violaceum*, PLP (1 mM), NAD^+ (1 mM), L-alanine (10 equiv), ammonium formate (150 mM), 11 U FDH, 12 U AlaDH; 26 h, 30 °C, 120 rpm. b) Pd/C, H_2, 4-15 h, RT; c) **1e** (0.5 mmol), (*R*)-ω-TA from *Arthrobacter* sp., PLP (1 mM), NAD^+ (1 mM), D-alanine (10 equiv), ammonium formate (150 mM), 11 U FDH, 12 U AlaDH; 26 h, 30 °C, 120 rpm.

6a,**b**,**d**,**e** were obtained in good yields and respectable optical purity (Scheme 3).[17]

In summary, the first regio- and stereoselective asymmetric monoamination of diketones was reported. Various 1,5-diketones were selectively transformed into optically pure amino ketones through the use of ω-transaminases. In the current study, the intermediate amino ketones obtained underwent a spontaneous ring-closure, to give Δ1-piperideines. Diastereoselective reduction of these products established a second chiral center, providing an efficient method for the preparation of chiral 2,6-disubstituted piperidines. Using this method, the shortest synthesis to date of the alkaloid (+)-dihydropinidine **6a**, and related piperidines, was achieved. This methodology expands the toolbox for regio- and stereoselective aminations, and is a step towards cleaner and more selective organic transformations.[18]

Experimental Section

Representative preparative example for the regio- and stereoselective biocatalytic amination and subsequent diastereoselective reduction:

(2*S*)-2-methyl-6-propyl-2,3,4,5-tetrahydropyridine ((2*S*)-**4a**): Lyophilized cells of *E. coli* containing overexpressed ω-TA from *C. violaceum* (225 mg) were rehydrated in a phosphate buffer (10 mL, pH 7.0, 100 mM) containing PLP (1 mM), NAD^+ (1 mM), ammonium formate (150 mM), FDH (11 U, 5 mg), AlaDH (12 U, 150 μL) and L-alanine (500 mM) at 22 °C for 30 min. Substrate **1a** (78 mg, 0.5 mmol) was added and the reaction was shaken at 30 °C for 26 h. Saturated aqueous Na_2CO_3 solution was added (1.00 mL) and the mixture extracted with small portions of EtOAc (4 × 5 mL). Combined organic layers were dried (Na_2SO_4), filtered, and employed in the next step without further purification. The product was obtained with >99% conversion in optically pure form (>99% *ee*) as judged by achiral and chiral GC.

(2*S*,6*R*)-2-Methyl-6-propyldihydropiperidine·HCl ((2*S*,6*R*)-**6a**·HCl): The crude solution containing (2*S*)-**4a** was treated with 10% palladium on activated charcoal (10 mg) at room temperature before a stream of hydrogen was bubbled through the solution for 4 h. After completion of the reaction, the solution was filtered through a pad of celite 545 and cooled to 0 °C. The product was crystallized by the addition of a solution of HCl in Et_2O. The HCl salt of the natural product dihydropinidine ((2*S*,6*R*)-**6a**·HCl) was obtained as a colorless solid in 94% yield (82 mg, 0.47 mmol, >99% *de*). ^1H and ^{13}C NMR data are in agreement with those previously reported.[15a] Melting point = 243–245 °C. Optical rotation: $[\alpha]_D^{20} = -12.2$ ($c = 0.5$; EtOH, >99% *de*). Literature value for the opposite enantiomer:[15d] $[\alpha]_D^{20} = +12.4$ ($c = 0.1$; EtOH, >99% *de*).

For further experimental details, analytical data, and full characterization of all products, see the Supporting Information.

Received: March 26, 2012
Published online: May 22, 2012

Keywords: alkaloids · asymmetric reductive amination · chiral piperidines · regioselectivity · ω-transaminases

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[16] a) J. Duchek, D. R. Adams, T. Hudlicky, *Chem. Rev.* **2011**, *111*, 4223 – 4258; b) R. M. Schmaltz, S. R. Hanson, C.-H. Wong, *Chem. Rev.* **2011**, *111*, 4259 – 4307; c) R. N. Patel, *ACS Catal.* **2011**, *1*, 1056 – 1074; d) T. Fischer, J. Pietruszka, *Top. Curr. Chem.* **2010**, *297*, 1 – 43.

[17] In the case of **1c**, several of the reduction conditions tested led to the opening of the cyclopropane ring. The cyclopropane ring stayed intact only when DIBAL was employed as the reducing agent; however, in this case, the conversion was very low (10–20%).

[18] a) R. Noyori, *Nat. Chem.* **2009**, *1*, 5 – 6; b) J. M. Woodley, *Trends Biotechnol.* **2008**, *26*, 321 – 327; c) H. E. Schoemaker, D. Mink, M. G. Wubbolts, *Science* **2003**, *299*, 1694 – 1697.

