Asymmetric Organocatalysis

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Kinetic Resolution of Oxazinones: An Organocatalytic Approach to Enantiomerically Pure β-Amino Acids**

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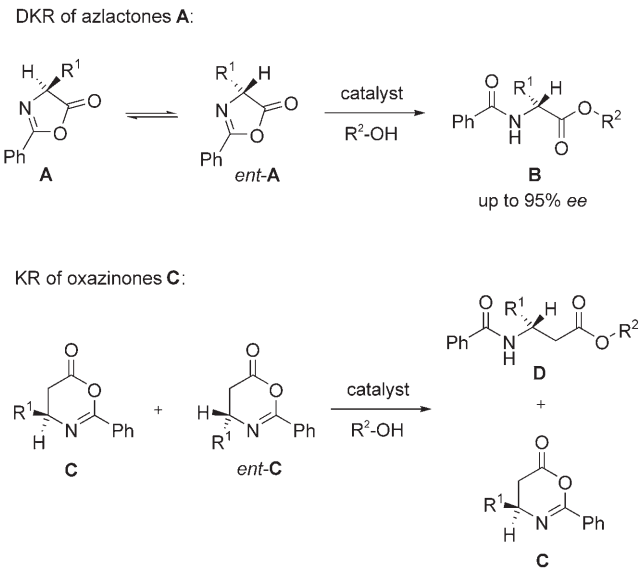
The development of new methods for the enantioselective synthesis of β-amino acids has been of considerable interest during the last years.[1–4] Owing to their unique pharmacological properties in the free form,[5] as cyclized β-lactams,[6] and as structural elements of naturally occurring compounds such as taxol[7] and the dolastatins,[8] there is a high demand in both academia and industry for enantiopure β-amino acids.[9] Besides chiral-auxiliary-based strategies[4] and catalytic asymmetric synthesis[1,10–13] the kinetic resolution of racemates is a well-established method for obtaining β-amino acids with high enantiomeric purity. The latter methodology is divided into "classical" chemical resolution processes, in which chiral resolving agents are used in stoichiometric amounts,[14] and enzymatic resolutions, which require acylases, amidases, or lipases.[15,16] Although the selectivity of enzymatic processes is in most cases excellent, the narrow substrate scope and thus the need for time-consuming enzyme engineering present a major drawback. To overcome these difficulties, we envisaged that the application of readily available modular organocatalysts[17] could greatly enhance the scope of these processes. Motivated by our success in the organocatalytic dynamic kinetic resolution (DKR) of azlactones *rac*-**A**, we set out to expand this methodology beyond the synthesis of (non-natural) α- to the even more challenging β-amino acids (Scheme 1).[18,19]

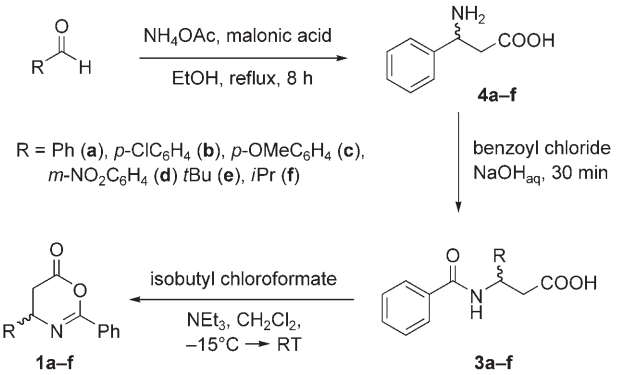
Azlactones **A** racemize readily and can be converted into the enantiomerically enriched N,C doubly protected α-amino acid derivatives **B**. By formally inserting a methylene group between the carbonyl group and the α-C atom of the azlactone, the nitrogen atom moves to the β position. The resulting compounds are known as 4,5-dihydro-1,3-oxazin-6-ones **C**, which are—in contrast to azlactones—configurationally stable. Although achiral and enantiomerically pure oxazinones **C** were utilized in peptide chemistry for coupling to amino acid esters,[20] no catalytic ring-opening reaction



Scheme 1. Alcoholytic DKR of azlactones (**A**, *ent*-**A**;top) and KR of oxazinones (**C**, *ent*-**C**; bottom).

appears to have been reported so far.[21] We considered these compounds to be promising substrates for organocatalytic asymmetric ring opening. It was hoped that the bifunctional thiourea catalysts **2a** and **2b** (Table 1), which proved to be highly effective in the alcoholytic DKR of azlactones,[19] would effect a kinetic resolution (KR) of racemic oxazinones.[22,23] If the selectivity of the catalyst is sufficiently high, a KR process will be of practical significance, provided that the racemate is obtained in an easy and cost-effective manner and that both the remaining and the converted substrate enantiomers are valuable compounds.[24] Oxazinones can be synthesized in a way similar to azlactones by cyclodehydration of the corresponding *N*-benzoyl amino acids **3** (Scheme 2).[25] We decided to use the one-step protocol of Tan and Weaver for the synthesis of racemic β-amino acids **4** from inexpensive aldehydes, malonic acid, and ammonium acetate (Scheme 2).[26]

The crude amino acids **4a–f** were converted directly into the *N*-benzoyl derivatives **3a–f** without the need for preceding purification. Condensation to give oxazinones **1a–f** was best effected by isobutyl chloroformate. Preliminary experi-



Scheme 2. Synthesis of the racemic oxazinones *rac*-**1a–f**.

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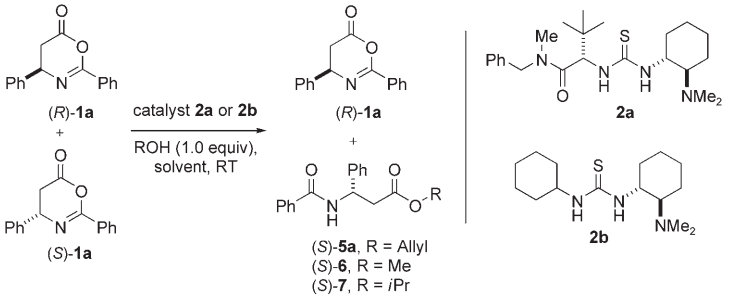
ments indicate that **1** can also be obtained directly in a single step from β-amino acids **4** by treatment with excess benzoyl chloride. The first experiments with 4,5-dihydro-2,4-diphenyl-1,3-oxazin-6-one (*rac*-**1a**) as substrate and allyl alcohol as nucleophile in the presence of the bifunctional thiourea **2a** (5 mol%) already showed the potential of this process. As expected for a kinetic resolution, the enantiopurity of the remaining oxazinone **1a** and the product ester **5a** is a function of the conversion (Figure 1).

At 57% conversion, the *S* enantiomer of the oxazinone substrate *rac*-**1a** is completely consumed (99% *ee* in favor of the remaining *R* enantiomer), and the enantiomeric excess of the product ester (*S*)-**5a** is 86% (Table 1, entry 3). Calculated from these kinetic data, the selectivity factor *S* of the reaction is 68. At a conversion lower than 45%, the ester is produced with more than 94% *ee* (Figure 1 and Table 1, entries 1 and 2). Slightly lower selectivity and activity were observed when using 5 mol% of the cyclohexyl-substituted catalyst **2b** (Table 1, entry 4). As a consequence we chose catalyst **2a** for all further experiments. Because

Table 1: Optimization of the reaction conditions



Entry	Catalyst loading [mol%]	Cat.	Solvent	Alcohol (R)	*t* [h]	Conv. [%][a]	*ee* (**1a**) [%][a]	*ee* (**5a–7**) [%][a]
1	5	**2a**	toluene	allyl	0.5	26	25	96
2	5	**2a**	toluene	allyl	1.5	45	58	94
3	5	**2a**	toluene	allyl	6.5	57	99	86
4	5	**2b**	toluene	allyl	12	59	97	81
5	10	**2a**	toluene	allyl	4.5	57	>99	84
6	2.5	**2a**	toluene	allyl	26	61	98	87
7[b]	1	**2a**	toluene	allyl	10	61	98	85
8	5	**2a**	THF	allyl	126	58	84	81
9	5	**2a**	DCM	allyl	24	66	>99	62
10	5	**2a**	CH_3CN	allyl	24	28	18	69
11	5	**2a**	toluene	Me	24	63	>99	71
12	5	**2a**	toluene	*i*Pr	24	4	<2	23

[a] Conversions and enantiomeric excesses were determined by chiral HPLC. [b] This reaction was carried out with a substrate concentration of 0.5 M; 0.1 M concentration in other reactions.

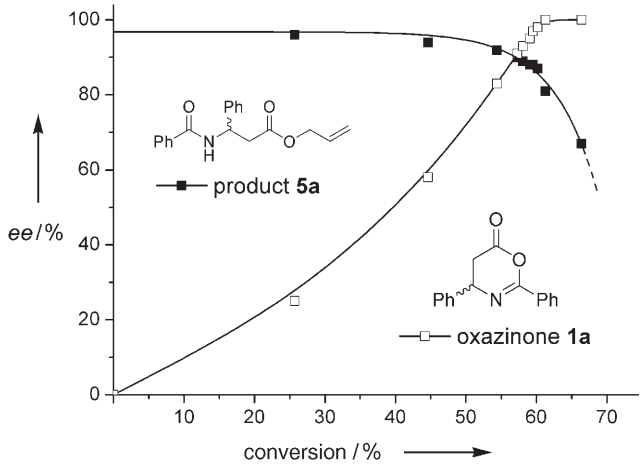
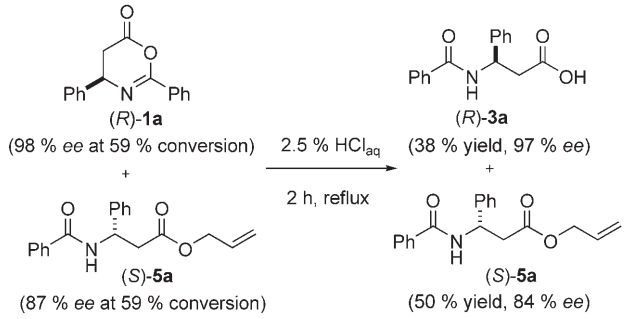


Figure 1. Time course of the kinetic resolution of *rac*-**1a** with allyl alcohol (1.0 equiv) and catalyst **2a** (5 mol% relative to *rac*-**1a**).

of the inherent difficulty in the accurate determination of selectivity factors when $S > 50$, we decided to characterize the quality of the kinetic resolution described herein solely in terms of conversion and *ee* values of the substrate and product, respectively (Table 1).[27]

The remaining oxazinone **1a** can be separated from the converted product ester **5a** by treating the reaction mixture with dilute aqueous HCl (Scheme 3; see Supporting Information for details). This hydrolytic procedure quantitatively converts the remaining oxazinone (*R*)-**1a** into the insoluble *N*-benzoyl β-amino acid (*R*)-**3a**. There is virtually no loss in



Scheme 3. Hydrolytic work-up procedure for the separation of the resolved oxazinone (*R*)-**1a** from the product ester (*S*)-**5a**.

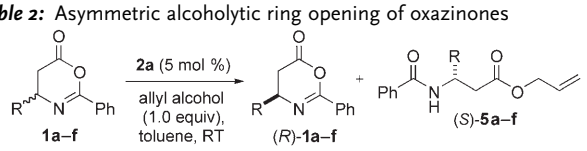
enantiomeric purity during this hydrolysis reaction (Scheme 3). The filtrate contains the pure ester product (*S*)-**5a**.

An increase in the catalyst loading to 10 mol% decreased the reaction time to 4.5 h, without affecting the selectivity (Table 1, entry 5). At a catalyst loading of 2.5 mol%, the reaction time is longer but the selectivity remains virtually unaffected (Table 1, entry 6). This decrease in the reaction rate could be compensated for by raising the concentration of the substrates from 0.1 to 0.5 M. Under these conditions, a catalyst loading of only 1 mol% was sufficient to catalyze the reaction effectively (Table 1, entry 7). Comparison with authentic samples prepared from enantiomerically pure (*S*)-3-amino-3-phenylpropanoic acid allowed us to determine the absolute configuration of both the oxazinone **1a** and the ester product **5a** by chiral HPLC.

An increase in the solvent polarity, for example, by changing from toluene to THF or acetonitrile, retarded the reaction quite significantly (Table 1, entries 8 and 10). Based on the assumption that hydrogen bonds between the catalyst and the substrate are crucial for the activation of the latter, this effect can be rationalized by the ability of THF to act as a competing hydrogen-bond acceptor. In the case of acetonitrile, hydrogen bonds are weakened by dipolar interaction with the solvent. In dichloromethane (DCM) the reaction proceeded with a satisfying rate, but the selectivity was somewhat lower (Table 1, entry 9). Prolonged reaction times resulted from the variation of the alcohol nucleophile to methanol or 2-propanol (Table 1, entries 11 and 12). In the case of methanol, the reaction was still practically useful, although the selectivity was somewhat lower. In contrast, the sterically more demanding 2-propanol reacts much more slowly. Only 4% conversion was observed after 24 h (Table 1, entry 12).

To demonstrate the broad substrate scope of our KR process, we chose the electron-poor *p*-chlorophenyl- and *m*-nitrophenyl-substituted oxazinones **1b** and **1d** as well as the electron-rich *p*-methoxyphenyl-substituted oxazinone **1c** as substrates (Table 2, entries 2, 4, and 3). Furthermore, to show

Table 2: Asymmetric alcoholytic ring opening of oxazinones



Entry	Substrate (R)	*t* [h]	Conv. [%][a]	*ee* (**1**) [%][a,b]	*ee* (**5**) [%][a]
1	**1a** (Ph)	6.5	57	99	86
2	**1b** (*p*-ClC_6H_4)	15	59	99	83
3	**1c** (*p*-$OMeC_6H_4$)	10.5	57	98	87
4	**1d** (*m*-$NO_2C_6H_4$)	3.0	64	99	81
5	**1e** (*t*Bu)	48	54	97	82
6	**1f** (*i*Pr)	48	53	98	88

[a] Conversions were determined by chiral HPLC, the enantiomeric excesses either by chiral HPLC or chiral GC. [b] The absolute configurations of the products **1b–f** were assigned by analogy to **1a**.

that the method is not limited to oxazinones with aromatic substituents, we also included the *tert*-butyl derivative **1e** and the isopropyl derivative **1f** (Table 2, entries 5 and 6) in our study. We were pleased to see that all substrates were resolved with a high degree of enantioselectivity. In the presence of catalyst **2a** (5 mol%), the oxazinones **1a–f** were generally obtained with excellent enantiomeric excess (Table 2), whereas the esters were still produced with 80–90% *ee*.

Comparison of **1a** with the *p*-chlorophenyl-substituted oxazinone **1b** and the *p*-methoxy-substituted oxazinone **1c** reveals that the enantioselectivity is not significantly affected by the substituent on the aromatic ring (Table 2, entries 1–3). The same holds for the oxazinone **1d**, which bears a nitro substituent in the *meta* position (Table 2, entry 4). With the latter substrate, the reaction is complete within only 3 h. The sterically more-demanding *tert*-butyl residue and the isopropyl group of oxazinones **1e** and **1f** are also tolerated at reaction times of 48 h (Table 2, entries 5 and 6). The latter two examples demonstrate that the procedure is not limited to β-amino acids with aromatic substituents but can also be used equally well for the enantioselective synthesis of alkyl-substituted derivatives.

In summary, we have described a novel and practical organocatalytic method for the synthesis of enantiomerically pure β-amino acids. To the best of our knowledge, this is the first time that oxazinones were applied in a catalytic ring-opening reaction. The resolutions are carried out at ambient temperature; the applied catalyst is modular, readily available, and can be used at loadings as low as 1 mol%. This process provides efficient access to highly valuable protected β-amino acids from inexpensive bulk chemicals. The resolved starting material and the product can be separated by filtration in a simple workup procedure. It is particularly noteworthy that the remaining enantiomerically pure oxazinones are activated β-amino acid derivatives that can, in principle, be applied directly in coupling reactions, for example, in the synthesis of β-peptides. The scope of this novel resolution process and its mechanism are currently under investigation.

Experimental Section

All commercially available chemicals were used without further purification. (*S*)-3-Amino-3-phenylpropionic acid was a gift from Degussa AG, Hanau. Solvents were distilled prior to use and dried, if necessary, by using standard techniques. HPLC analysis was performed on Merck–Hitachi HPLC equipment with HPLC-grade solvents from Fisher Scientific. GC analysis was performed on Hewlett-Packard equipment. Catalysis runs were carried out under inert atmosphere.

Resolution of oxazinones: The alcohol nucleophile (1.00 equiv) was added to a solution of the catalysts **2a** or **2b** (8.33 μmol, 0.05 equiv) in absolute toluene (670 μL). After the addition of a solution of the oxazinone **1a–f** (167 μmol, 1.00 equiv) in absolute toluene (1.00 mL), the homogeneous reaction mixture was stirred at ambient temperature. For analysis, 50-μL samples were withdrawn and diluted with acetonitrile (450 μL). The conversion and enantiomeric excess were determined immediately by HPLC or GC (see Supporting Information). Quantification was based on UV detection at $\lambda = 230$ nm. The conversion was determined by comparison with the peak areas of stock solutions of the oxazinones **1** and the corresponding *N*-benzoyl amino acid esters **5–7** in dichloromethane.

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