Second-generation organocatalysts for the highly enantioselective dynamic kinetic resolution of azlactones

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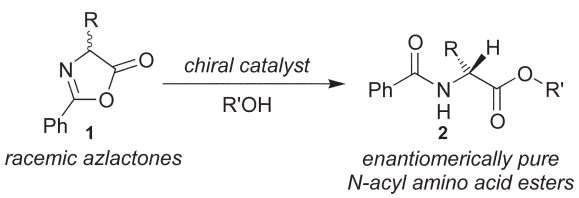
Bifunctional organocatalysts of the thiourea-*tert*-amine type, carrying two "matched" elements of chirality, effect the alcoholytic dynamic kinetic resolution of a variety of azlactones with up to 95% ee.

Enantiomerically pure natural and non-natural α-amino acids find numerous applications in the synthesis of chiral ligands, catalysts, pharmaceuticals, peptides and many other valuable target molecules. Therefore, the development of practical methods for the enantioselective synthesis of α-amino acids is a challenging task, in particular for non-natural amino acids.[1] Besides asymmetric synthesis, the dynamic kinetic resolution (DKR) of suitable racemic precursors is a very practical avenue leading to the desired enantiomerically pure product in (theoretically) quantitative yield.[2]

In the area of α-amino acids, the alcoholytic dynamic kinetic resolution of azlactones **1** is an attractive way to generate the enantiomerically enriched and *N*,*C*-doubly protected α-amino acid derivatives **2** (Scheme 1). Azlactones racemize readily, but only a few examples of chemically catalyzed DKRs of azlactones appear to exist.[3] The planar-chiral DMAP-derivatives by Fu *et al.* represented the most efficient catalysts, affording a maximum ee of 78%, albeit at the expense of very long reaction times.[3c]

Recently, we applied (*inter alia*) the (thio)urea-based bifunctional organocatalyst **3a** for this purpose and achieved significantly improved enantioselectivities, *e.g.* 91% ee at −20 °C in the reaction of the *tert*-leucine-derived azlactone (**1**, R = *t*-Bu, Scheme 1) with allyl alcohol.[4] NMR-spectroscopic studies indicated that the catalyst activates the azlactone by hydrogen bonding of the quasi-*Lewis*-acidic (thio)urea moiety to the carbonyl oxygen atom.[4] The alcohol nucleophile is activated and steered by the *Brønsted*-basic tertiary amine. Here we report the use of the catalysts **3b–8** (Scheme 2) in the dynamic kinetic resolution of azlactones. With the exception of **3b** and **3c**, these second generation catalysts harbour an additional element of chirality



Scheme 1 Alcoholytic DKR of racemic azlactones.

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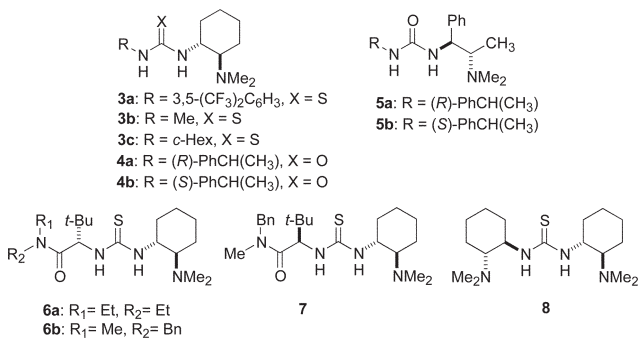
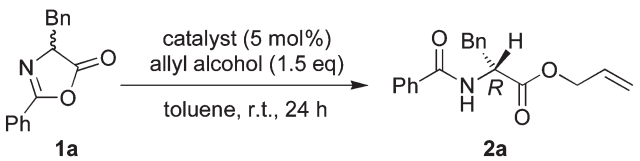


Scheme 2 Urea/thiourea-based bifunctional organocatalysts.

(besides the chiral diamine moiety). As it turned out, excellent enantioselectivities were achieved even at room temperature.

Our previous work was based on urea/thiourea catalysts carrying an electron-poor aromatic moiety on the urea nitrogen atom (as in **3a**).[4] In the first stage of the current study, we examined a series of bifunctional organocatalysts bearing simple aliphatic (**3b, c**) or chiral benzylic substituents (**4a, b**) on the urea/thiourea nitrogen atom. The DKR of the phenylalanine-derived azlactone **1a** served as the test reaction (Table 1). To our surprise, we found that the methyl substituted catalyst **3b** showed comparable reactivity and higher enantioselectivity for the ring

Table 1 Optimization of catalyst structure



Entry	Catalyst	Conversion (%)	ee[a] (%)
1	**3a**	90	51
2	**3b**	81	67
3	**3c**	96	75
4	**4a**	87	74
5	**4b**	70	76
6	**5a**	27	73[b]
7	**5b**	22	47[b]
8	**6a**	76	73
9	**6b**	59	78
10	**7**	24	59
11	**8**	84	76

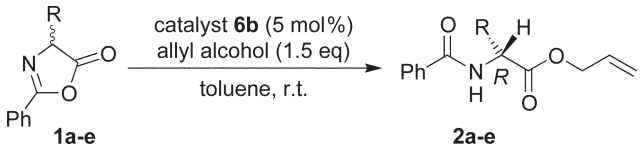
[a] Conversion and ee determined by chiral HPLC. [b] (*S*)-Enantiomer formed in excess.

opening of the Phe-derived azlactone **1a** with allyl alcohol (Table 1, entry 2). Replacement of the methyl group by a cyclohexyl group (**3c**) increased both reactivity and selectivity (entry 3). Incorporation of a 1-phenethyl group furnished the two diastereomeric catalysts **4a**, **4b**, none of them showing enhanced selectivity (Table 1, entries 4, 5). The same holds for the diastereomeric catalysts **5a, b** which, in addition, showed fairly low activity (entries 6, 7). The latter observation demonstrates the importance of the rigid diamine scaffold. In summary, it appears that the sense of stereoinduction is determined predominantly by the absolute configuration of the chiral diamine. It is interesting to note that the C_2-symmetric thiourea **8** showed selectivity comparable to **3c** (Table 1, entries 3, 11).

We expected further enhancement in selectivity by increasing the steric demand at the additional chiral centre. For this purpose, we synthesized the *tert*-leucine amide-derived catalysts **6a**, **6b** and **7** (Scheme 2). The *tert*-leucine amide motif was employed previously by Jacobsen *et al.* in the design of chiral organocatalysts.[5] To our delight we found that the catalyst **6b** indeed furnished 78% ee, which is the highest enantioselectivity ever achieved in the chemically catalyzed DKR of the Phe-azlactone **1a**. The X-ray crystal structure of the related catalyst **6a** (Fig. 1)† aids in rationalizing the improved selectivity: We assume that the chiral information present at the "left" end of the thiourea moiety enhances the stereodifferentiation effected by the diaminocyclohexane moiety. Clearly, changing from *N*,*N*-diethyl to *N*-methyl-*N*-benzyl in **6b** makes the latter effect even more pronounced, and thus explains the improved selectivity of **6b** over **6a**. In line with the above argument, the "mismatched" diastereomer **7** (derived from D-*tert*-leucine) of **6b** provides significantly lower enantioselectivity and activity (Table 1, entry 10).

In order to demonstrate the general applicability of the catalyst **6b**, we screened several azlactones **1a–e** derived both from natural and non-natural α-amino acids. The results are summarized in Table 2. In all cases, the enantiomeric excesses were higher than 75%, using 5 mol% of the catalyst **6b** at room temperature. For the valine-, *tert*-leucine- and leucine-derived azlactones **1c–e**, excellent enantiomeric purities of the resulting *N*-benzoylamino acid allyl esters **2c–e** were obtained (Table 2, entries 3–5). In the case of the *tert*-leucine derived azlactone **1d**, the product ester **2d** was obtained with 95% ee which marks a significant improvement compared to all other catalysts studied.[3,4] Lowering the reaction temperature from ambient to −20 °C resulted in even higher enantioselectivity (*ca.* 99% ee), but also in unacceptably slow conversion (*ca.* 5% after 48 h). At room temperature, the reactions go to completion without drop in enantioselectivity in all cases, indicating the dynamic character of these kinetic resolutions. In addititon to the reaction times listed in Table 2, 96 h were required to achieve > 90% conversion in the case of the Leu-azlactone **1e**. For the *t*-Leu-azlactone **1d**, 63% conversion was achieved after 7 d.

Table 2 Substrate screening using the thiourea catalyst **6b**



Entry	Substrate (R)	Time/h	Conversion[a] (%)	ee[a,b] (%)
1	**1a** ($PhCH_2$)	48	77 (98)	78 (77)
2	**1b** (Me)	24	94	80
3	**1c** (*i*-Pr)	48	59 (89)	92 (90)
4	**1d** (*t*-Bu)	48	28	95
5	**1e** (*i*-Bu)	48	77	91

[a] The values in parentheses were obtained for catalysis using 1.7-fold concentrations of the substrates and catalyst. [b] Enantiomeric excess was determined by chiral HPLC analysis.

The initial rates of substrate conversion in the DKR of the Phe-azlactone (**1a**) with allyl alcohol, using the three catalysts **3a**, **3c** and **6b** are compared in Fig. 2. The order of reactivity is **3c** > **3a** > **6b**. When a relative rate (k_{rel}) of 1 is assigned to the most enantioselective catalyst **6b**, the bis(trifluoromethyl)phenyl-substituted thiourea **3a** shows a k_{rel} of 1.43. The cyclohexyl-substituted thiourea **3c** is more than twice as fast as **6b** (k_{rel} = 2.14).

Please note that our organocatalytic[6] DKR can also be applied to the clean *stereoinversion* of natural and non-natural α-amino acids. For example, the azlactone **1d** prepared from

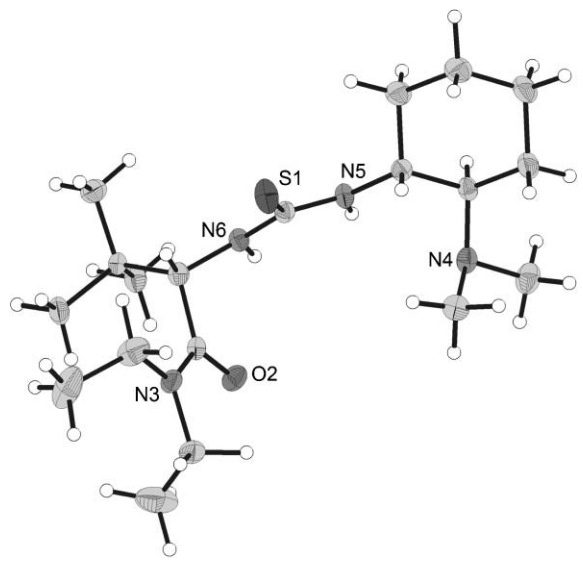


Fig. 1 X-Ray crystal structure of the thiourea catalyst **6a** (ORTEP).

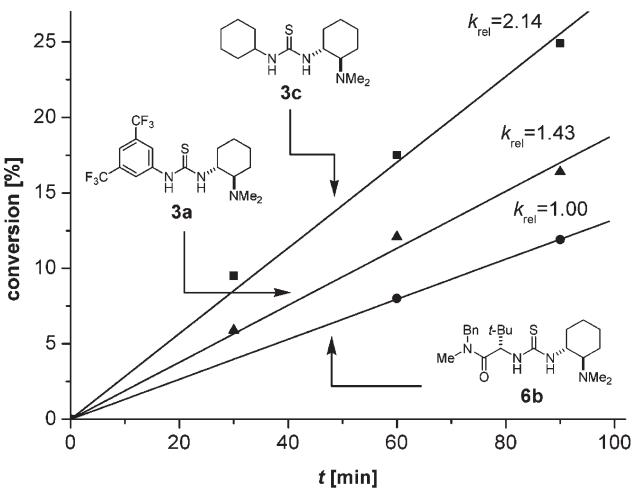


Fig. 2 Initial rates of substrate conversion in the DKR of the Phe-azlactone (**1a**) with allyl alcohol (rt, 5 mol% catalyst).

enantiomerically pure L-*tert*-leucine gave the *N*-benzoyl-D-*tert*-leucine allyl ester **2d** after alcoholytic DKR with catalyst **6b**.

In summary, we have described a method for the alcoholytic DKR of azlactones effected by the organocatalyst **6b**, providing direct access to a wide range of protected natural and non-natural α-amino acids in high enantiomeric excess. The catalyst is readily accessible from commercially available starting materials. Experiments to reveal the precise mechanism of this catalytic process are currently underway in our laboratory and will be the subject of further reports.‡

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Notes and references

† *Crystal data* for **6a**: $C_{19}H_{38}N_4OS$, $M = 370.59$, colourless needles, 0.30 × 0.30 × 0.25 mm, monoclinic, $a = 11.702(1)$, $b = 13.351(1)$, $c = 14.156(1)$ Å, $\beta = 100.81(1)^\circ$, $V = 2172.4(3)$ Å^3, $T = 100(2)$ K, space group $P2_1$, $Z = 4$, $\rho_{calcd.} = 1.133$ g cm^{-3}, $\mu = 0.163$ mm^{-1}. A total of 10636 reflections were measured, 8211 unique, final residuals were $R1 = 0.0439$ and $\omega R2 = 0.0887$ for 6520 observed reflections with $I > 2\sigma(I)$, 756 parameters, GOF = 1.023, maximum residual electron density 0.308 e Å^{-3}, absolute structure parameter −0.05(5). Data were collected on a Nonius KappaCCD diffractometer ($2\Theta_{max} = 54^\circ$, $Mo_{K\alpha}$-radiation ($\lambda = 0.71073$ Å), graphite monochromator, φ/ω scans). The structure was solved by using direct methods,[7] followed by full-matrix least-squares refinement (using all unique reflections) with anisotropic thermal parameters for C, N, O, S and isotropic parameters for H.[8] CCDC 256348. See http://www.rsc.org/suppdata/cc/b4/b418666d/ for crystallographic data in .cif or other electronic format.

‡ *Typical procedure for the DKR of azlactones*: To a solution of 8.33 μmol of the catalyst (0.05 eq) in 667 μl abs. toluene, 1.5 eq of allylic alcohol was added. After addition of a solution containing 167 μmol of the azlactone (1.00 eq) in 1.0 ml abs. toluene, the homogeneous reaction mixture was stirred at ambient temperature. For analysis, 100 μl samples were withdrawn, diluted with 900 μl dichloromethane, and conversion and enantiomeric excess were determined immediately by HPLC (Daicel Chiralpak AD or Merck (*S*,*S*)-Whelk O1, *n*-hexane/2-propanol). Quantification was based on UV detection at $\lambda = 230$ nm and 210 nm, respectively. Conversion was determined by comparison with the peak areas of stock solutions of the azlactones and the corresponding *N*-benzoyl amino acid esters in dichloromethane.

1 (*a*) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer and T. Zelinski, *Angew. Chem.*, 2004, **116**, 806; M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer and T. Zelinski, *Angew. Chem. Int. Ed.*, 2004, **43**, 788; (*b*) H. Gröger and K. Drauz, in *Asymmetric Catalysis on Industrial Scale*, eds. H. U. Blaser and E. Schmidt, Wiley-VCH, Weinheim, 2004, p. 131.

2 (*a*) H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249; (*b*) K. Faber, *Chem. Eur. J.*, 2001, **7**, 5004; (*c*) H. Pellissier, *Tetrahedron*, 2003, **59**, 8291.

3 (*a*) K. Gottwald and D. Seebach, *Tetrahedron*, 1999, **55**, 723; (*b*) L. Xie, W. Hua, A. S. C. Chan and Y.-C. Leung, *Tetrahedron: Asymmetry*, 1999, **10**, 4715; (*c*) J. Liang, J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 3154.

4 A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller and J. Lex, *Angew. Chem.*, 2005, **117**, 817; A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller and J. Lex, *Angew. Chem. Int. Ed.*, 2005, **44**, 807. Catalysts of the thiourea-*tert*-amine type were applied before by Takemoto *et al.* for asymmetric aza-Henry reactions and Michael additions: T. Okino, S. Nakamura, T. Furukawa and Y. Takemoto, *Org. Lett.*, 2004, **6**, 625; T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2003, **125**, 12672.

5 (*a*) G. D. Joly and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 4102; (*b*) M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 10558; (*c*) A. G. Wenzel and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 12964; (*d*) P. Vachal and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 10012; (*e*) A. G. Wenzel, M. P. Lalonde and E. N. Jacobsen, *Synlett*, 2003, 1919.

6 A. Berkessel and H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, 2005.

7 G. M. Sheldrick, *SHELXS-97, Program for the Solution of Crystal Structures*, University of Göttingen, Germany, 1997.

8 G. M. Sheldrick, *SHELXL-97, Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, 1997.

