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The Efficient Enantiodivergence of (*dl*)-1,3-Diacetyl-2-imidazolidinethiones by Enantioselective Catalytic Deacetylation

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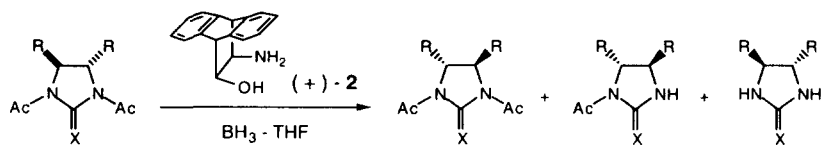
Abstract : An enantioselective borane-mediated deacylation of C_2- symmetrical 1,3-diacetyl-2-imidazolidinethiones, catalyzed by oxazaborolidines derived *in situ* from an aminoalcohol **2** and borane, provides a promising process for highly effective kinetic resolution.

The chiral 2-imidazolidinones and 2-imidazolidinethiones constitute efficient and versatile auxiliaries,[1] which are as reactive as the widely employed 2-oxazolidinone auxiliaries.[2] Considerable interest exsists for versatile catalytic processes for the chiral preparation of such heterocyclic auxiliaries. Recently, we have shown that the effective asymmetrization of sterically congested *meso*-1,3-diacyl-2-imidazolidinones leading to powerful chiral auxiliaries can be readily achieved in a catalytic manner *via* enantioselective borane-mediated monodeacetylation, catalyzed by conformationally rigid oxazaborolidines, which are derived *in situ*, from the type **2** aminoalcohol and borane.[3] This is based on the inherent reactivity of 1,3-diacyl-2-imidazolidinone heterocycles which undergo extremely facile monodeacylation with negligible full deacetylation under nucleophilic conditions.

We wish to report herein a catalytic process for the kinetic resolution of (*dl*)-C_2-symmetrical 1,3-diacetyl-2-imidazolidinones **1a** and -imidazolidinethiones **1b** by a borane-mediated reductive deacetylation catalyzed by the chiral, conformationally rigid, sterically congested aminoalcohol **2**. The heterocycles examined in this study involved the most frequently used C_2-symmetrical 4,5-diphenyl and 4,5-tetramethylene-2-imidazolidinone type auxiliaries (**6** and **10**), which would also serve as good precursors of the highly



(*dl*) - **1a, b** (**a** : X = O, **b** : X = S) (***R, R***) - **3a, b** (***R, R***) - **4a, b** (***S, S***) - **5a, b**

Scheme 1

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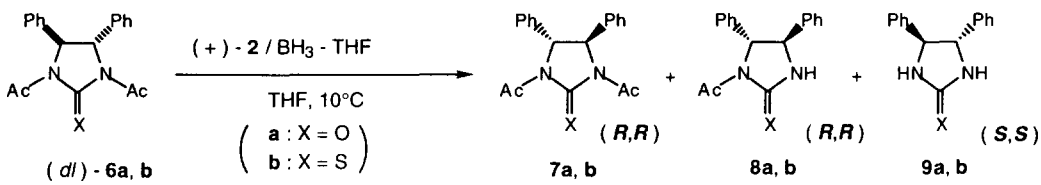
versatile *trans*-1,2-diamine ligands.[4] This reagent system has been successfully employed for the enantioselective reductions of prochiral ketones to secondary alcohols.[5]

Thus, the kinetic optical resolution of *trans*-4,5-diphenyl-2-imidazolidinone **6a** and the corresponding thione **6b** to the promising chiral 2-imidazolidinone type auxiliaries was explored as a typical probe.

A solution of (*dl*)-1,3-diacetyl-2-imidazolidinone[6] **6a** in THF was treated with borane-THF complexes (1.0 equiv) in the presence of a catalytic amount of (+)-aminoalcohol[7] **2** (10 mol%) at 20 °C for 2.5h. Partial reductive deacetylation occured, giving the (*R,R*)-diacetate **7a** (94 %ee) in 41% yield, but efforts to effectively isolate the deacetylated (*S,S*)-isomer **9a** in a high enantiomer excess failed, due to contamination with inseparable products.

However, (*dl*)-1,3-diacetyl-4,5-diphenylimidazolidinethione **6b** was readily reductively deacetylated on treatment with borane-THF in the presence of (+)-aminoalcohol **2** (5-10 mol%) at 10 °C to cleanly give (*4R,5R*)-1,3-diacetyl-2-imidazolidinethione **7b**, (*4R,5R*)-1-acetyl-2-imidazolidinethione **8b** and (*4S,5S*)-2-imidazolidinethiones **9b** with excellent enantioselectivity above 95 %ee in satisfactory yields.[8] The borane-THF complexes constituted the choice of reducing reagents, since the use of dimethylsulfide complexes resulted in lower levels of enantioselection, and triethylamine- and pyridine- complexes were much less reactive under the conditions employed herein. The imidazolidinethiones **7b**-**9b** thus formed were readily separable by chromatography on silica gel and the stereochemistry was determined by comparison with authentic species derived from (*S,S*)- and (*R,R*)-1,2-diphenylethylenediamines. The oxazaborolidines derived from the

Table 1. Enantioselective Deacetylation of (*dl*)-1, 3-Diacetyl-4, 5-diphenyl-2- imidazolidinone (6a) and the Thione (6b) by Borane-reduction Catalyzed by Oxazaborolidines [a]

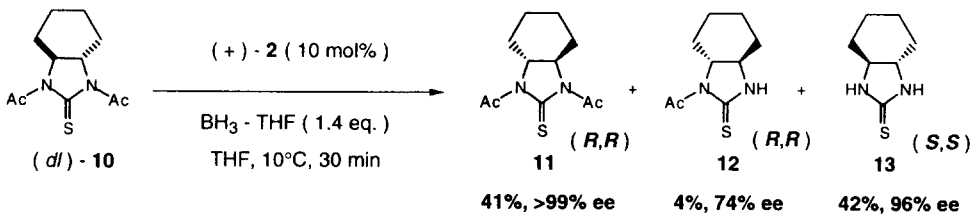


Compound 6 (X)	Aminoalcohols (mol%)	BH_3-complex (equiv.)	Time (h)	Yield [b] 7 (%ee)[c]	8 (%ee)[c]	9 (%ee)[c]
6a (O)	**2** (10)	BH_3-THF (1.0)	2.5[d]	41% (94)	-	28% (-)[e]
6b (S)	**2** (5)	BH_3-THF (0.95)	1	35% (>99)	13% (96)	50% (95)
6b (S)	**2** (10)	BH_3-SMe_2 (1.0)	2.5[d]	44% (78)	20% (4)	27% (99)
6b (S)	**2** (10)	BH_3-THF (1.0)	0.5	34% (>99)	16% (93)	48% (94)
6b (S)	**DPPM**[f] (10)	BH_3-THF (1.0)	4	84% (1)	9% (9)	-

a) For reaction conditions, see Text.[8] b) Isolated yield. c) Determined by HPLC. d) Performed at 0-20 °C.
e) Not determined due to the presence of an inseparable impurity. The yield was estimated by NMR.
f) α,α-Diphenyl-2-pyrrolidinemethanol.

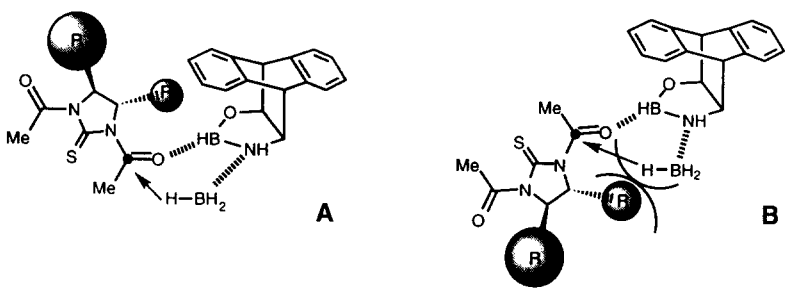
aminoalcohol, α,α-diphenyl-2-pyrrolidinemethanol (DPPM),[9] were not effective catalysts for this type of kinetic resolution. These results are summarized in **Table 1**.

The versatility of this procedure for kinetic resolution was provided by another example, namely, (*dl*)-1,3-diacetyl-4,5-tetramethylene-2-imidazolidinethiones **10** which underwent enantio-differentiating deacetylation in a similar manner to give (*4R,5R*)-1,3-diacetyl-2-imidazolidinethiones **11** and (*4S,5S*)-2-imidazolidinethiones **13** with excellent enantioselectivity and yield, along with the monoacetyl product **12** with moderate selectivity (**Scheme 2**).

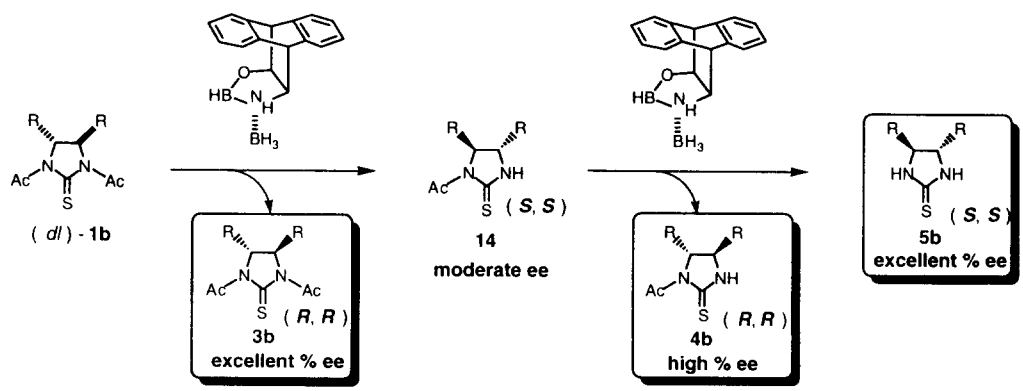


Scheme 2

An enantiodifferentiating mechanism similar to that presented for the enantioselective reduction of ketones[5,10] appears to be operative in these reactions, and the less hindered transition forms **A** rather than the **B** forms would result in the preferential deacylation of the (*S,S*)-isomers.



This enantioselective deacetylation method is practical and interesting, since both enantiomers have been obtained in excellent enantioselectivity and yield in a single procedure. This may be rationalized by taking into



Scheme 3

account the double enantiodivergence which consists of continuous enantiodifferentiating deacylations of (*dl*)-diacetyl-**1b** and the enantiomerically enriched monoacetyl-2-imidazolidinethiones **14** (**Scheme 3**). Since it is well known that the 2-imidazolidinethiones are readily convertible to 2-imidazolidinones by treatment with mercuric acetate,[11] the catalytic enantiodivergence process described here is highly promising for the practical preparation of C_2-symmetrical chiral 2-imidazolidinones and the thiones, which serve as versatile chiral auxiliaries, as well as building blocks for chiral *vic*-diamines of biological and synthetic interest. Further study of the scope and limitations of this method are now underway.

References and Notes

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6. The racemic 2-imidazolidinone **6a** and the thiones **6b** and **11** were preparaed from commercially available *trans*-1,2-diphenyl-1, 2-diaminoethane and *trans*-1,2-diaminocyclohexane, according to the literature.[11]
7. Aminoalcohol (+)-**2**: this was prepared by ring-opening of the 2-oxazolidinone auxiliary (-)-**DHAOx**[12] with $Ba(OH)_2$, mp 187.5-188.5 °C (from hexane), $[\alpha]_D^{29}$+26.0° (*c* 1.00, $CHCl_3$), ^{1}H-NMR (500 MHz / $CDCl_3$) δ :0.59 (3H, s), 2.15 (3H, br), 3.33 (1H, dd, *J* = 3.1, 7.9 Hz), 3.85 (1H, dd, *J* = 3.1, 7.9 Hz), 4.18 (1H, d, *J* = 3.1 Hz), 4.42 (1H, d, *J* = 3.1 Hz), 7.00-7.40 (8H, m).
8. **Typical procedure for enantioselective deacetylation**: A solution of (+)-**2** (0.15 mmol) and BH_3• THF (0.3 mmol) in THF (25 ml) was stirred at 25 °C for 15min and a solution of **6b** (1.5 mmol) in THF (15 ml) was then added at 0 °C. To the mixture, a 0.2*M* solution of BH_3 • THF (1.2 mmol) in THF was added dropwise to this mixture over a period of 30 min, followed by stirring at 10 °C for an additional 30 min. Acidification with a 2*N*-HCl solution, followed by the usual work-up gave (*R*, *R*)-**7b** (>99% ee) in 34%, and (*R*, *R*)-**8b** (93% ee) in 165%, and (*S*, *S*)-**9b** (94% ee) in 48% yields. The optical purity was determined as the 1,3-diacetates by HPLC analysis on a Chiralcel OD-H column.
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