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CATALYTIC PROCESS FOR EFFICIENT ENANTIODIVERGENCE OF *MESO-N,N'*-DIACETYL-2-IMIDAZOLIDINONES AND *DL-N*-ACETYL-2-OXAZOLIDINONES

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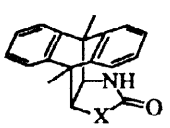
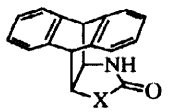
Abstract : A reductive monodeacylation, catalyzed by oxazaborolidines derived from conformationally rigid chiral aminoalcohols provideds a practical method for the effective enantiodivergence of *meso*-1,3-diacetyl-2-imidazolidinones. This catalytic deacylation is successfully applied to the kinetic resolution of racemic 1-acetyl-2-oxazolidinones.

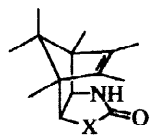
Sterically congested and conformationally fixed 2-oxazolidinones[1] and 2-imidazolidinones[2] such as the tricyclic compounds **1-5** have proven to be excellent chiral auxiliaries for use in highly enantiocontrolled carbon-carbon bond formation. The conventional method for the preparation of such types of chiral heterocycles involves an optical resolution step using (1*S*,2*R*)-2-methoxy-1-apocamphanecarboxylic acid (MAC-acid),[3] which is efficient, but tedious and time-consuming. An alternative procedure which has recently been reported for the enantiodivergence of 1,3-diacetyl-2-imidazolidinones also requires stoichiometric amounts of the chiral reagent **7** as the lithium salts.[2] As a result, there is an ongoing need for a practical method for the large scale preparation of such types of chiral 2-imidazolidinone and 2-oxazolidinone auxiliaries *via* a catalytic process.



1 (X=O, DMAOx)
2 (X=N-R, DMAIm)

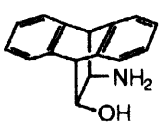


3 (X=O, DHAOx)
4 (X=N-R, DHAIm)



5 (X=O, HMCOx)
6 (X=N-R, HMCIm)

We wish to report herein a catalytic procedure for the efficient enantiodivergence of *meso*-1, 3-diacetyl-2-imidazolidinones and *dl*-1-acetyl-2-oxazolidinones by a borane-mediated reductive mono-deacetylation, which is catalyzed by the sterically constrained 2-aminoalcohols, **7** and **8**, which are, in turn, readily prepared by the ring-opening of the chiral 2-oxazolidinone auxiliaries, **3** and **5**, respectively.



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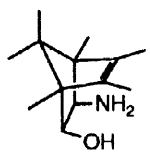

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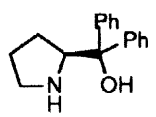

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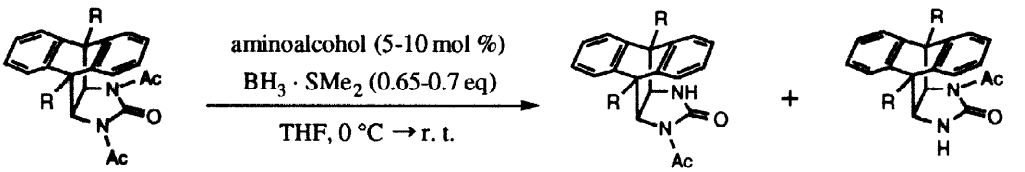
PII: S0040-4039(98)01340-9

We recently reported that the conformationally ridid tricyclic oxazaborolidines, derived from *cis*-fixed (+)-aminoalcohols **7** and **8**, have great potential as efficient catalysts for the enantioselective borane-reduction of ketones.[4] This borane-mediated reduction has been successfully applied to the enantioselective monodeacylation of *meso*-1,3-diacyl-2-imidazolidinones, derived from the cycloaddition of 1,3-diacyl-2-imidazolones to anthracenes, and which can be readily monodeacylated.[2]



10a, b a) R =H, b) R=Me **11a, b** **12a, b**

Scheme 1

Thus, the borane-mediated monodeacetylation of *meso*-1,3-diacetyl-2-imidazolidinone **10a** (R=H) proceeded smoothly at room temperature to give (+)-1-acetyl-2-imidazolidinone **11a**[5] with excellent enantioselectivity, in excess of 99% ee, when (+)-aminoalcohol **7** (5-10 mol%) was used as a catalyst, in combination with borane-methyl sulfide complexes. In a similar manner, the more bulky *meso*-compound **10b** (R=Me) also underwent smooth monodeacetylation to give (+)-1-acetyl-2-imidazolidinone **11b**[6] with 98% ee. The stereochemistry of the **11a** and **b**, which are preferentially formed has been previously established.[2] The sterically more congested (+)-aminoalcohol **8** was moderately effective, as seen in **Table 1**, while the *B*-methyl oxazaborolidine[7] derived from (*S*)-α, α-diphenyl-2-pyrrolidinemethanol (**9**) and trimethylboroxine was much less effective as a catalyst. Thus, the aminoalcohol **7** appears to be the chiral reagent of choice for

Table 1 Enantioselective Monodeacetylation of *Meso*-1, 3-Diacetyl-2-imidazolidiones (10a, b) Catalyzed by Oxazaborolidines Derived from Aminoalcohols (7, 8)

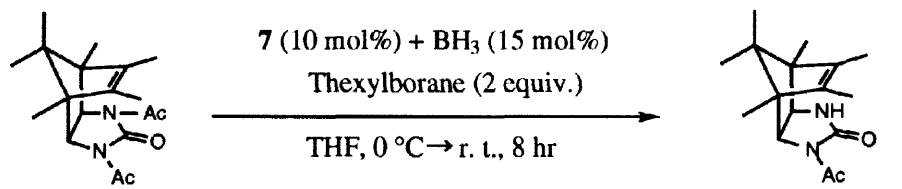
R (**10**)	Aminoalcohol (mol %)	Borane (equiv.)	Time (h)	Yield (%)[a]	% ee[b]
H	**7** (10)	BH_3 (0.7)	2	74	99 (**11a**)
	7 (5)	BH_3 (0.65)	2	69	99 (**11a**)
	8 (10)	BH_3 (0.7)	4	31	90 (**11a**)
	9 (10)[c]	BH_3 (0.6)	4	9	78 (**12a**)
	7 (10)	BH_3 (0.15) +thexylborane (2)	8	78	99 (**11a**)
Me	**7** (10)	BH_3 (0.7)	2	71	98 (**11b**)
	7 (10)	BH_3 (0.15) +thexylborane (2)	8	81	98 (**11b**)

a) Isolated yield. b) Determined by HPLC analysis. c) With the *B*-methyl oxazaborolidine derived from **9** and trimethylboroxine.

the enantiodivergence of *meso*-**10**.

This reductive deacetylation was accompained, as expected, by the formation of by-products such as *N*-ethyl- and *N*, *N'*-diethyl-2-imidazolidinones in 5-10% yield, depending on the reaction conditions. When the more bulky reducing agent, thexylborane, was used in place of BH_3-complexes, the side reactions were greatly suppressed, resulting in negligible amounts of the *N*-ethyl compounds. Under the modified conditions and employing thexylborane in the presence of catalytic amounts of BH_3-complexes, the yield was appreciably improved with no decrease in enantioselectivity (**Table 1**).[8] The optically active 1-acetyl-2-imidazolidinones **11a** and **b** thus obtained, after purification by a single recrystallizaition, serve as excellent precursors for chiral 2-imidazolidinone auxiliaries as has been recently demonstrated.[2]

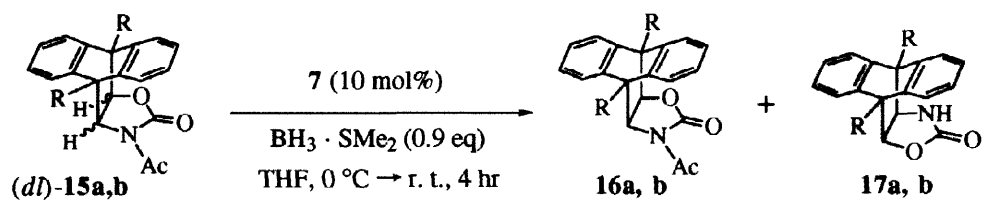
This reducing system was sufficiently effective to permit the facile monodeacetylation of diacetyl-imidazolidinone **13** without affecting olefinic function, thus providing a good precursor **14**[9] for the chiral auxiliaries **6** with excellent enantioselectivity, in excess of 98% ee (**Scheme 2**).



13 **14** 98% ee (81%)

Scheme 2

Interestingly, this catalytic deacylation process was versatile enough to permit the kinetic optical resolution of the racemic 3-acetyl-2-oxazolidinones. Thus, the cycloadduct **15b** (R=Me) derived from 3-acetyl-2-oxazolone and 9, 10-dimethylanthracene was treated with 0.9 equimolar amounts of borane-methyl sulfide complexes in the presence of the chiral aminoalcohol **7** (10 mol%) at room temperature for 4 h to give (+)-*N*-acetyl-2-oxazolidinone **16b**[10] in 99% ee in 41% yield, in addition to the deacetylated derivative **17b** in 72% ee in 56% yield. The use of less amounts of the borane complex (0.6 equiv.) considerably enhanced the enantioselectivity of **17b**, up to 90% ee, but in a reduced yield (below 20%). Exceptionally large differences in the rate between the enantiomers clearly demonstrate the potential of this method for nonenzymatic kinetic resolution. In a similar manner, the anthracene-derived cycloadduct **15a** (R=H) gave **16a**[11] in 98% ee, as seen in **Scheme 3**.



(*dl*)-**15a,b** **16a, b** **17a, b**

a) R=H	98% ee (40 %)	71% ee (43 %)
b) R=Me	99% ee (41 %)	72% ee (56 %)

Scheme 3

In both cases, the formation of 3-ethyl-2-oxazolidinones, as might be expected, were not detected.

Deacylation of the **16a** and **b** thus obtained with cesium carbonate followed by single recrystallization

gave, respectively, the pure 2-oxazolidinone auxiliaries, (+)-DHAOx[1a] and (+)-DMAOx.[1b]

In conclusion, the catalytic monodeacylation process presented here is highly practical for the preparation of versatile chiral tricyclic auxiliaries, and may be applicable to the facile synthesis of chiral building blocks for *vis*-diamine and *vic*-aminoalcohol skeletons which are found in a substantial number of bioactive compounds.

REFERENCES AND NOTES

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2. Yokoyama, K. : Ishizuka, T. : Kunieda, T. *Tetrahedron Lett.*, **1998**, in press.
3. **Ishizuka**, T. : Kimura. K. : Ishibuchi, S. : Kunieda, T. *Chem. Lett.*, **1992**, 991.
4. **Hashimoto**, N. : Ishizuka, T. : Kunieda, T. *Heterocycles*, **1997**, *46*, 189.
5. **11a** (R=H): mp 245.0 °C (from EtOH), $[\alpha]_D$ +123.3 ° (*c* 1.0, $CHCl_3$).
6. **11b** (R=Me): mp 235.0 °C (from MeOH), $[\alpha]_D$ +165.2 ° (*c* 1.0, $CHCl_3$).
7. Corey, E. J. : Bakshi, R. K. : Shibata, S. : *J. Am. Chem. Soc.* **1987**, *109*, 555.
8. **Typical procedure for enantioselective monodeacylation** :
   a) To a stirred solution of **7** (0.05 mmol) and $BH_3{\cdot}SMe_2$ (0.1 mmol) in THF (2 ml) was added a solution of **10a** (0.5 eq) and $BH_3{\cdot}SMe_2$ (0.25 mmol) in THF (4 ml) at 0 °C under an atmosphere of argon. After stirring for 2h at room temperature, the mixture was acidified with 3*N* HCl. The usual work-up, followed by chromatographic purification, gave (+)-1-acetyl-2-imidazolidinone **11a**, in 74% yield whose optical purity was determined to be 99% ee by HPLC analysis on a Chiralcel OD-H column.
   b) A solution of **7** (0.05 mmol) and $BH_3{\cdot}SMe_2$ (0.1 mmol) in THF (2 ml) was stirred at room temperature for 15 min. and **10b** (0.5 mmol) was then added at 0 °C. To the mixture, a 0.4 *M* solution of thexylborane (1 mmol) in THF was added dropwise, followed by stirring at room temperature for 8 h. The work-up, as above, gave an 81% yield of **11b** in 98% ee.
9. **14** : mp 154.0 °C (from hexane), $[\alpha]_D$ +161.2° (*c* 1.0, $CHCl_3$), ^{1}H-NMR (500 MHz / $CDCl_3$) δ : 5.86 (1H, brs), 4.63 (1H, d, *J*=8.5 Hz), 3.75 (1H, d, J=8.5 Hz), 2.42 (3H, s), 1.58 (3H, s), 1.49 (3H, s), 1.03 (3H, s), 0.73 (3H, s), 0.63 (3H, s). The absolute configuration is tentatively assigned, based on comparison with **11a** and **b**.
10. **16b** (R=Me) : mp 213 °C (from hexane-CH_2Cl_2), $[\alpha]_D$ +204.8° (*c* 1.0, $CHCl_3$), ^{1}H-NMR (270 MHz / $CDCl_3$) δ : 7.32 (8H, m), 4.62 (1H, d, *J*=8.4 Hz), 4.49 (1H, d, *J*=8.4 Hz), 2.41 (3H, s), 2.09 (3H, s), 1.93 (3H, s).
11. **16a** (R=H) : mp 171 °C (from hexane-CH_2Cl_2), $[\alpha]_D$ +163.6° (*c* 1.0, $CHCl_3$), ^{1}H-NMR (270 MHz / $CDCl_3$) δ : 7.32 (8H, m), 5.05 (1H, d, *J*=3.5 Hz), 4.78 (1H, dd, *J*=3.5, 8.5 Hz), 4.68 (1H, d, *J*=3.5 Hz), 4.55 (1H, dd, *J*=3.5, 8.5 Hz), 2.32 (3H, s).