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Facile Enantiodivergence of *meso*-1,3-Diacyl-2-imidazolidinones to Chiral 2-Imidazolidinone Auxiliaries

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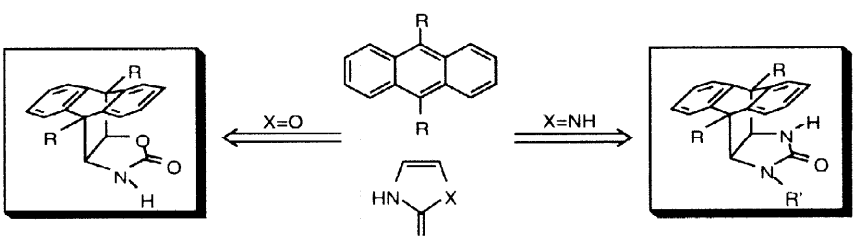
Abstract: The enantioselective monodeacylation of *meso*-1,3-diacetyl-2-imidazolidinones, by treatmenmt with the lithium salts of sterically constrained *N,N* - dimethylaminoalcohol gives 1-acetyl-2-imidazolidinones in 89% ee. The latter compounds serve as good precursors for efficient chiral auxiliaries.

Chiral 2-imidazolidinones, as well as 2-oxazolidinones,[1] which are widely used as chiral auxiliaries, hold considerable promise, because of their high stability and versatility.[2] By analogy with the preparation of the tricyclic 2-oxazolidinones (**1a**[3a], **b**[3b]) which we previously developed as excellent chiral auxiliaries, a similar type of chiral 2-imidazolidinone skeletons (**2a**, **b**), which are conformationally rigid and sterically congested, have been found to be readily formed by the smooth cycloaddition of the simple heterocycle, 2-imidazolone,[4] to the anthracenes, followed by facile optical resolution with the aid of MAC-acid.[5] Thus, the synthetic procedures employed for the chiral 2-oxazolidinone auxiliaries (**1a**, **b**) are quite applicable to the facile preparation of both enantiomers of 2-imidazolidinones (**2**).[5]



1a R=H : DHAOx
1b R=Me : DMAOx

2a R=H : DHAIm
2b R=Me : DMAIm

This paper describes an alternative and somewhat simple route to such optically active 2-imidazolidinones (**2a**, **b**) which serve as highly potent chiral auxiliaries. The method involves, as a key step, the chemically efficient discrimination between two enantiotopic acyl groups of *meso*-1, 3-diacyl-2-imidazolidinones (**3a**, **b**) which are highly susceptible to monodeacylation with mild bases, such as cesium carbonate and aliphatic amines.

Thus, an equimolar solution of 1, 3-diacetyl-2-imidazolone and anthracene or 9,10- dimethylanthracene in xylene was heated at 130 °C to give the 1, 3-diacetyl-2-imidazolidinones (**3a**, **b**)[6] in 69-93% yield.

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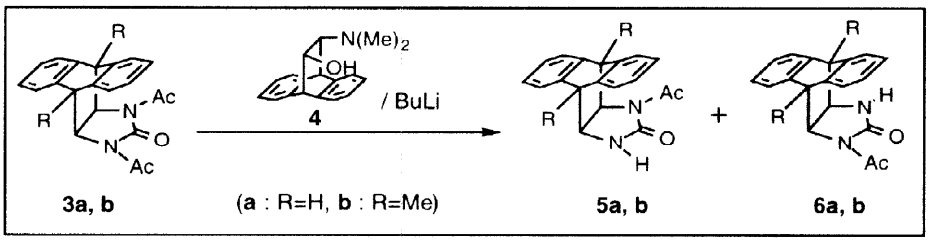
Monodeacetylation of the *meso*-compounds thus obtained proceeded smoothly in the presence of tertiary amines at 0 °C with a high level of enantioselection on treatment with the lithium salts of chiral dimethylaminoalcohol **4**,[7] which is primarily characterized by its steric congestion and conformational rigidity (**Scheme 1**).



Scheme 1

Table 1. Enantioselective Monodeacylation of *meso*-1, 3-Diacetyl-2-imidazolidinones with Alkoxides[a)]

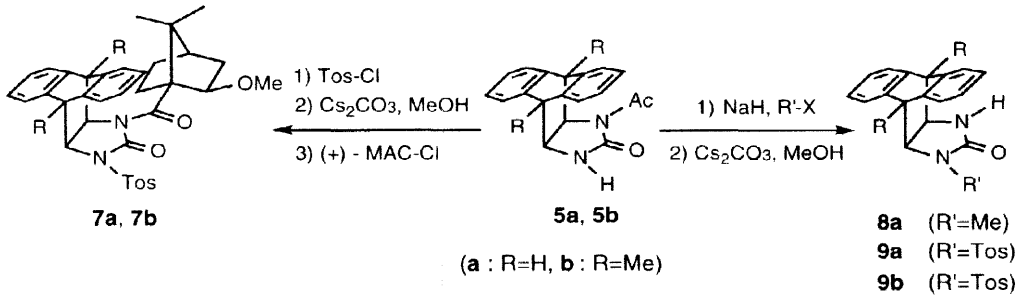
Compound	**4** (eq.)	Base (eq.)	Additive (eq.)	Temp., Time	Yield (%)	**5** : **6**[b)]	% ee
3a	(1.1)	BuLi (1)	none	0 °C, 1 h	60	2 : 1	35
3a	(1.1)	BuLi (1)	THF (solvent)	0 °C, 1 h	73	4 : 1	63
3a	(1.1)	BuLi (1)	quinuclidine (10), LiF (0.55)	0 °C, 1 h	70	10 : 1	82
3a	(1.1)	BuLi (1)	TED[c)] (10), LiF (0.55)	0 °C, 10 min	47	17 : 1	89
3a	(2.2)	BuLi (2)	TED (20), LiF (1.1)	0 °C, 1 h	83	15 : 1	88
3b	(1.1)	BuLi (1)	TED (10), LiF (0.55)	0 °C, 13 h[d)]	95	10 : 1	82
3a	(1.0)	$ZnEt_2$ (1)	none	100 °C, 4 h	60	1 : 4	62
3a	(1.0)	$ZnMe_2$ (1)	none	100 °C, 4 h	85	1 : 6	67

a) The reaction was performed in toluene. b) Determined by HPLC. c) TED : 1,4-diazabicyclo[2.2.2]octane. d) Performed in toluene-CH_2Cl_2 (3 : 1).

A solution of the *meso*-compound **3a** was treated with the lithium alkoxides, generated *in situ* from BuLi and a slight excess of dimethylaminoalcohol **4** in toluene at 0 °C to give monoacetyl derivative **5a** with 35% ee in addition to the acetate of **4**. The selectivity of this reaction could be improved up to 63% ee by the use of THF as solvent. Among the additives explored, including metal salts and tertiary amines, the combination of LiF and cyclic tertiary amines such as quinuclidine and TED in toluene solvent was the most effective for enhancing enantioselectivity, as summarized in **Table 1**. Thus, under optimal conditions using TED, the reaction gave enantiomer **5a**[8] in 88-89% ee, which was readily purified by a single recrystallization. In a similar manner, the more bulky dimethylanthracene-based imidazolidinone **3b** was also smoothly monodeacylated to give an excellent yield of **5b**[8] in 82% ee, followed by a recrystallization to give the optically pure forms. The absolute stereochemistry was unequivocally verified by chemically correlating **5a** and **5b** with the *N*-MAC-imidazolidinones **7a** and **7b**, respectively, whose structures have been determined by X-ray analysis[9] (**Scheme 2**).

Interestingly, a reversal of stereoselection in the enantioselective monodeacylation of **3a** was observed when dialkylzinc agents were used in place of BuLi, and enantiomer **6a** was obtained with a moderate enantioselectivity of 67% ee.

The use of (+)-cinchonine and (-)-cinchonidine in place of **4** resulted in monodeacylation with much lower level of enantioselection (20-30% ee).

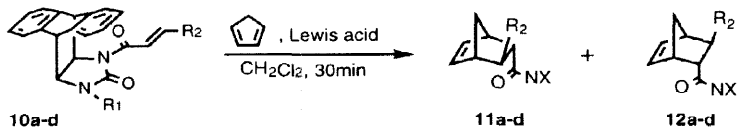


Scheme 2

The present method provides a practical route for good precursors of chiral 2-imidazolidinone auxiliaries. Thus, the *N*-methyl (**8a**) and *N*-tosyl-2-imidazolidinones (**9a, b**),[10] which were readily obtained from **5a** and **5b**, served well as excellent chiral auxiliaries, as is shown for a series of reactions (**Tables 2** and **3**).

The *N*-acylated compounds (**10a-d** and **13a-e**) were derived from the 2-imidazolidinone auxiliaries (**8a** and

Table 2. Diastereoselective Diels-Alder Reaction of *N*-Crotonyl and *N*-Acryl-2-imidazolidinones with Cyclopentadiene



Compound :	R_1	R_2	Lewis acid (eq.)	Temp. (°C)	Yield (%)	Σendo : Σexo[a]	**11** : **12**[a]
10a :	Me	Me	Et_2AlCl (1.4)	-30[b]	72	41 : 1	40 : 1
10b :	Tos	Me	Et_2AlCl (1.4)	-78	98	86 : 1	26 : 1
10c :	Me	H	Et_2AlCl (1.4)	-78	98	74 : 1	>500 : 1
10d :	Tos	H	Et_2AlCl (0.3)	-78	97	43 : 1	17 : 1
10d :	Tos	H	$BF_3 \cdot OEt_2$ (0.3)	-78	97	46 : 1	12 : 1

a) Determined by HPLC. b) The reaction was extremely sluggish at -78 °C.

Table 3. Diastereoselective Alkylation of *N*-Propionyl and *N*-Butyryl-2-imidazolidinones *via* Enolates

Compound :	R_1	R_2	R_3	RX	Yield (%)	**14** : **15**[a]
13a :	H	Me	H	CH_2=$CHCH_2Br$	99	10 : 1
13b :	H	Tos	H	CH_2=$CHCH_2Br$	80	160 : 1
13c :	H	Me	Me	CH_3I	80	2 : 1
13d :	H	Tos	Me	CH_3I	73	9 : 1
13e[b] :	Me	Tos	Me	CH_3I	46	89 : 1

a) Determined by HPLC. b) Performed at -50 °C.

9a, **b**) by smooth acylation with the appropriate acid chlorides.

In the Diels-Alder reaction with cyclopentadiene (**Table 2**), the *N*-tosyl-2-imidazolidinones (**10b**, **d**) were generally more reactive than the *N*-methyl derivatives (**10a** and **c**) which required higher reaction temperature (above -30 °C). Thus, the reaction with **10d** smoothly proceeded even in the presence of 0.3 equimolar amounts of Lewis acids, while the corresponding 2-oxazolidinone derivative was found to be much less reactive under the similar conditions.[11]

In the alkylations (**Table 3**), the *N*-tosyl auxiliaries (**9a** and **b**) were much superior in enhancing diastereoselectivity to the *N*-methyl compound (**8a**). It is noteworthy that diastereoselectivity appears to be highly dependent on the *N*-substituent groups of the 2-imidazolidinone auxiliaries, as suggested.

Mechanistic details should await further study.

References and Notes

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5. The optical resolution was readily achieved via facile separation of the diastereomeric *N*-MAC derivatives, **16** and **17**.
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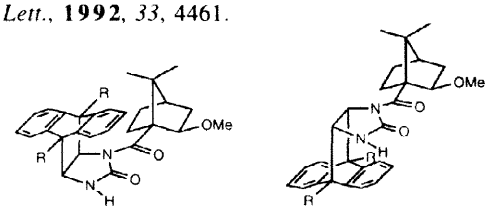

16a, b (**a** : R=H, **b** : R=Me) **17a, b**

6. **3a** : mp 216-217°C (from CH_2Cl_2-EtOH), ^{1}H-NMR (400MHz / $CDCl_3$) δ : 2.37 (6H, s), 4.45 (2H, t, J=1.5Hz), 5.06 (2H, m), 7.15-7.26 (6H, m), 7.40-7.43 (2H, m).
   3b : mp 260-261°C (from CH_2Cl_2-EtOH), ^{1}H-NMR (400MHz / $CDCl_3$) δ : 1.93 (6H, s), 2.39 (6H, s), 4.63 (2H, s), 7.23-7.43 (8H, m).
7. Kimura, K. ; Sugiyama, E. ; Ishizuka, T. ; Kunieda, T. *Tetrahedron Lett.*, **1992**, *33*, 3147.
8. **5a** : mp 244-245°C (from EtOH), $[\alpha]_D^{29}$-122.4° (*c* 1.00, $CHCl_3$), ^{1}H-NMR (400MHz / $CDCl_3$) δ : 2.35 (3H, s), 3.95 (1H, dd, J=3.3, 9.5Hz), 4.35 (1H, d, J=3.3Hz), 4.57 (1H, dd, J-2.9, 9.5Hz), 5.11 (1H, d, J-2.9Hz), 5.50 (1H, s), 7.15-7.31 (7H, m), 7.41-7.43 (1H, m).
   5b : mp 234-235°C (from MeOH), $[\alpha]_D^{29}$-165.2° (*c* 1.00, $CHCl_3$), ^{1}H-NMR (400MHz / $CDCl_3$) δ : 1.92 (3H, s), 1.94 (3H, s), 2.41 (3H, s), 3.72 (1H, d, J=9.2Hz), 4.66 (1H, d, J=9.2Hz), 5.23 (1H, s), 7.20-7.42 (8H, m).
9. We are much indebted to Research Laboratories, Yoshitomi Pharmaceutical Industreis, Ltd., Fukuoka, Japan, for the X-ray analysis.
   X-ray crystal data for **7a** [(mp 121-122°C (from Hexane), $[\alpha]_D^{27}$-22.6° (*c* 1.00, $CHCl_3$)] : $C_{35}H_{36}N_2O_5S$, monoclinic, *C*2, *a*=27.705(2) Å, *b*=7.967(2) Å, *c*=25.057(2) Å, β=117.61(1)°, *V*=4901(1) Å^3, *Z*=4, μ=0.585mm^{-1}, *R*=0.054.
   7b [(mp 255-256°C (from CH_2Cl_2-Hexane), $[\alpha]_D^{27}$-15.5° (*c* 1.00, $CHCl_3$)] : $C_{37}H_{40}N_2O_5S$, orthorhombic, $P2_12_12_1$, *a*=12.599(2) Å, *b*=23.557(2) Å, *c*=10.718(1) Å, *V*=3180.9(7) Å^3, *Z*=4, μ=1.24mm^{-1}, *R*=0.039.
   The authors have deposited atomic coordinates for **7a** and **7b** with the Cambridge Crystallographic Data Center. They can be obtained, on request, from the Director of the Center.
10. **8a** : mp 284-285°C (from CH_2Cl_2-Hexane), $[\alpha]_D^{28}$-6.9° (*c* 1.02, MeOH). **9a** : mp >300°C (from CH_2Cl_2-EtOH), $[\alpha]_D^{29}$+107.2° (*c* 0.50, MeOH). **9b** : mp 170-171°C (from Et_2O), $[\alpha]_D^{27}$+135.6° (*c* 1.00, MeOH).
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