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Sterically Constrained Tricyclic 2-Oxazolidinone as Excellent Chiral Auxiliary

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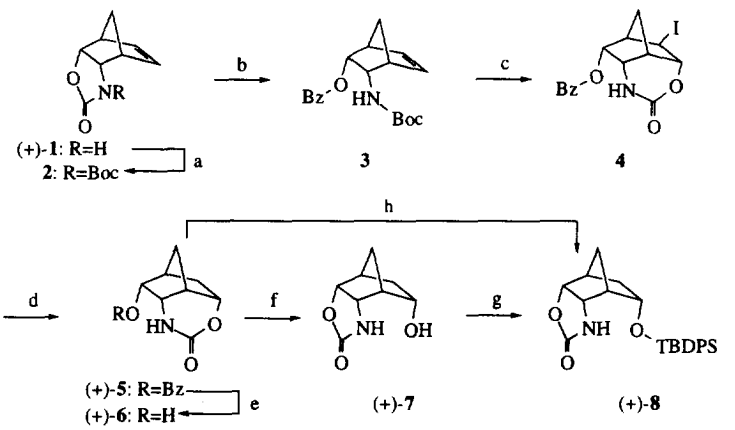
Abstract: A new class of conformationally rigid 2-oxazolidinones with effectively bulky substituents, derived from the [4+2] cycloadduct of cyclopentadiene and 2-oxazolone, serve as extremely powerful chiral auxiliaries for asymmetric alkylations, Diels-Alder reactions and conjugate addition reactions. © 1997, Elsevier Science Ltd. All rights reserved.

Stereochemically constrained chiral heterocycles, such as camphorsultams[1] and 2-oxazolidinones[2] have been stoichiometrically used as popular and reliable tools in the preparation of optically active compounds in high states of purity. In previous studies,[3] we introduced conformationally rigid chiral tricyclic 2-oxazolidinone auxiliaries derived from the Diels-Alder *endo*-adducts of 2-oxazolone and cyclic dienes such as cyclopentadiene and anthracene. Among these, compound **1** and its saturated derivative were of only limited use as chiral auxiliaries because of low chiral induction.[3a] This paper describes the structural modification of the parent 2-oxazolidinone (**1**) to give a new class of 2-oxazolidinones which contain bulky protecting-groups and which could be applied as a chiral auxiliary to achieve extremely enhanced asymmetric induction.

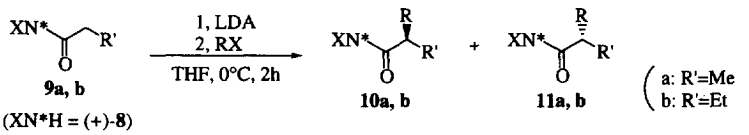


a) Et_3N, DMAP, $(Boc)_2O$, THF, r.t., 1h, 100%; b) PhLi, THF, -78°C, 10min, 95%; c) I_2, CH_2Cl_2, r.t., 7h, 63%; d) AIBN, Bu_3SnH, benzene, reflux, 7h, 81%; e) Cs_2CO_3, MeOH, r.t., 1.5h, 100%; f) NaH, DMF, r.t., 1.5h, 95%; g) BuLi, TBDPSCl, -78°C to r.t., 3h, 85%; h) NaH, TBDPSCl, DMF, r.t., 1.5h, 99%

Scheme 1

Scheme 1 outlines the synthetic route to the newly designed 2-oxazolidinone **8** which should effectively shield an enantiomeric face of five-membered heterocycle. Thus, *N*-protection of (+)-**1**[3a] with a Boc group, followed by ring cleavage, gave high yield of the protected amino alcohol (**3**). Halocyclization with I_2 gave the 6-membered tetrahydrooxazinone (+)-**4**, followed by reductive dehalogenation to give (+)-**5**. Deacylation of **5**, followed by treatment with NaH resulted in the smooth rearrangement to the-2-oxazolidinone (+)-**7**. Treatment of (+)-**6** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of NaH gave a quantitative yield of the desired (+)-**8**[4] in a single step.

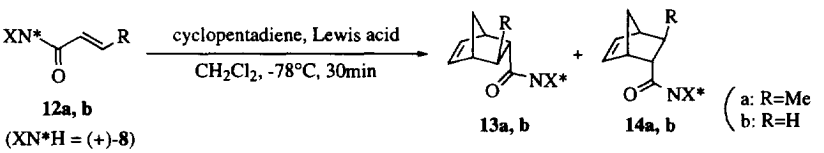
Table 1. Diastereoselective Alkylations of Chiral *N*-Propionyl- and *N*-Butyryl-2-oxazolidinones (**9**)



Entry	**9** (R')	RX	Yield (%)	**10** : **11** [a]
1	**9a** (Me)	$PhCH_2Br$	99	>500:1 [b]
2	**9a** (Me)	$CH_2=CHCH_2Br$	100	>500:1 [c]
3	**9b** (Et)	CH_3I	100	300:1 [c]

a) Determined by HPLC using a YMC-Pack SIL column. b) The stereochemistry was determined by conversion to (*R*)-2-methyl-3-phenylpropanol. c) The products were correlated with the authentic compounds prepared from (+)-**8** and the corresponding carboxylic acids.

Table 2. Diastereoselective Diels-Alder reactions of Chiral *N*-Alkenoyl-2-oxazolidinones (**12**)



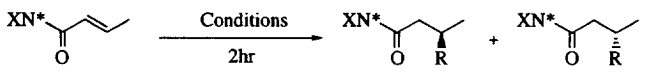
Entry	**12** (R)	Lewis acid (eq.)	Yield (%)	Σ *endo* : Σ *exo*	*endo* d.s. **13** : **14** [a]
1	**12a** (Me)	Et_2AlCl (1.4)	100	99:1	>500:1 [b]
2	**12a** (Me)	$BF_3{\cdot}Et_2O$ (1.4)	0	-	-
3	**12b** (H)	Et_2AlCl (1.4)	100	40:1	6:1 [c]
4	**12b** (H)	$BF_3{\cdot}Et_2O$ (1.4)	93	64:1	50:1
5	**12b** (H)	$BF_3{\cdot}Et_2O$ (0.5)	80	65:1	93:1

a) Determined by HPLC using a YMC-Pack SIL column. b) The authentic samples were prepared from (+)-8 and the carboxylic acids of known configuration.[2d] c) The stereochemistry was determined by reductive conversion ($LiBH_4$/MeOH) to the known alcohol.[2d]

The utility of this sterically congested 2-oxazolidinone as a chiral auxiliary was typically demonstrated by alkylation of the lithium enolates (**Table 1**), Diels-Alder reactions with cyclopentadiene (**Table 2**) and conjugate addition reactions with organocuprates (**Table 3**). Alkylation of the lithium enolates derived from *N*-propionyl-2-oxazolidinone (**9a**), with benzyl bromide and allyl bromide proceeded with excellent diastereoselectivity above 99.6% d.e. (Entries 1 and 2). Even for methylation, a reaction which is difficult to achieve with high diastereoselectivity,[5] excellent diastereoselectivity in excess of 99.3% d.e. was observed (Entry 3).

Table 2 shows Lewis acid-catalyzed Diels-Alder reactions of *N*-crotonyl- and *N*-acryloyl-2-oxazolidinone derivatives (**12a** and **12b**) with cyclopentadiene. *N*-Crotonyl-2-oxazolidinone (**12a**) in the presence of Et_2AlCl gave excellent *endo* and diastereoselectivity (Entry 1), while $BF_3{\cdot}Et_2O$ was completely ineffective on the catalytic activity. Although *N*-acryloyl derivatives (**12b**) failed to give such a high stereoselectivity in the presence of Et_2AlCl, the use of $BF_3{\cdot}Et_2O$ in place of Et_2AlCl, considerably improved the selectivity (Entries 3 and 4).

Table 3. Diastereoselective Conjugate Additions of Cuprates to Chiral *N*-crotonyl-2-oxazolidinone



12a (XN*H = (+)-**8**) **15** **16**

Entry	R	Reagent (eq.)	Solvent	Temp. (°C)	Yield (%)	**15** : **16** [a]
1	Ph	CuCl (3.3), PhMgBr (6.0)	THF	-78	99	118:1[b]
2	Ph	CuCl (0.2), PhMgBr (2.5)	THF	-78	93	88:1
3	CH_2=$CHCH_2$	CuCl (3.3), CH_2=$CHCH_2MgCl$ (6.0)	THF	-30	85	33:1[c]
4	Pr	CuCl (3.3), PrMgBr (6.0)	THF	-30	93	1:1[d]
5	Pr	CuBr·SMe_2 (3.3), PrMgBr (6.0)	THF	-30	100	2:1
6	Pr	CuBr·SMe_2 (3.3), PrLi (6.0)	THF	-30	96	33:1
7	Bu	CuBr·SMe_2 (3.3), BuLi (6.0)	THF	-30	95	37:1[d]

a) Determined by HPLC using a YMC-Pack SIL column. b) The stereochemistry was determined by conversion ($LiBH_4$/MeOH) to (*R*)-3-phenylbutanol. c) The product was hydrogenated (Pd/H_2) to the dihydro derivative identical with the authentic compound prepared from (+)-**8** and (*S*)-3-methylhexanoic acid. d) The authentic compounds **15** (R=Pr) and **15** (R=Bu) were prepared from (+)-**8** and (*S*)-3-methylhexanoic acid and (*S*)-3-methylheptanoic acid, respectively.

Diastereoselective conjugate additions of *N*-crotonyl-2-oxazolidinone (**12a**) with organocuprates are shown in **Table 3**. Reactions with phenyl- or allylcuprates proceeded smoothly with high diastereoselectivity (Entries 1-3), while when **12a** was reacted with dipropylcuprates, the results were more complex. Reaction with the cuprates prepared from CuCl or CuBr·SMe_2 and propylmagnesium bromide in THF gave only low diastereoselectivity (Entries 4 and 5), while use of propyl- or butyllithium in the place of the Grignard reagent considerably improved the selectivity above 94% d.e. (Entries 6 and7). Excellent diastereoselectivity observed

is noteworthy, since it is generally difficult to control a Michael-type conjugate addition with high selectivity using the conventional 2-oxazolidinone auxiliary based methods.[6]

Quantitative removal of the 2-oxazolidinone auxiliary from the reaction products (**10**, **13** and **15**) described here was smoothly performed by treatment with $LiBH_4$/MeOH or LiOOH. Thus, newly introduced tricyclic 2-oxazolidinone (**8**) with the *t*-butyldiphenylsilyloxy substituent represents a highly promising skeleton as a chiral auxiliary and, at present, can be ranked as an efficient and reliable tool which is generally superior to recently developed DMAOx[3b] and HMCOx.[3c]

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4. (+)-**6**: mp 228.0 °C, $[\alpha]_D$ +15.8 °(*c* 0.3, CH_3OH), ^1H NMR (500MHz, CD_3OD) δ 1.46-1.55 (m, 2H), 1.81-1.85 (m, 1H), 1.96-2.02 (m, 1H), 2.22-2.24 (m, 1H), 2.37-2.38 (m, 1H), 3.59-3.62 (m, 1H), 4.02-4.05 (m, 1H), 4.75-4.82 (m, 1H)
(+)-**7**: mp 212.8 °C, $[\alpha]_D$ +17.6 °(*c* 1.0, CH_3OH), ^1H NMR (500MHz, CD_3OD) δ 1.32-1.36 (m, 1H), 1.46-1.50 (m, 1H), 1.53-1.56 (m, 1H), 1.95-2.01 (m, 1H), 2,42-2.43 (m, 1H), 2.56-2.58 (m, 1H), 4.02-4.05 (m, 1H), 4.33-4.38 (m, 1H), 4.89-4.92 (m, 1H),
(+)-**8**: mp 126.3 °C, $[\alpha]_D$ +1.6 °(*c* 1.0, $CHCl_3$), ^1H NMR (500MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.23-1.33 (m, 2H), 1.64-1.72 (m, 2H), 2.34-2.35 (m, 1H), 2.47-2.55 (m, 1H), 3.98-4.02 (m, 1H), 4.28-4.32 (m, 1H), 4.84-4.87 (m, 1H), 5.07 (br s, 1H), 7.36-7.48 (m, 6H), 7.61-7.67 (m, 4H).
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