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Kinetic Resolution of *sec*-Alcohols with Axially Chiral Twisted Amides

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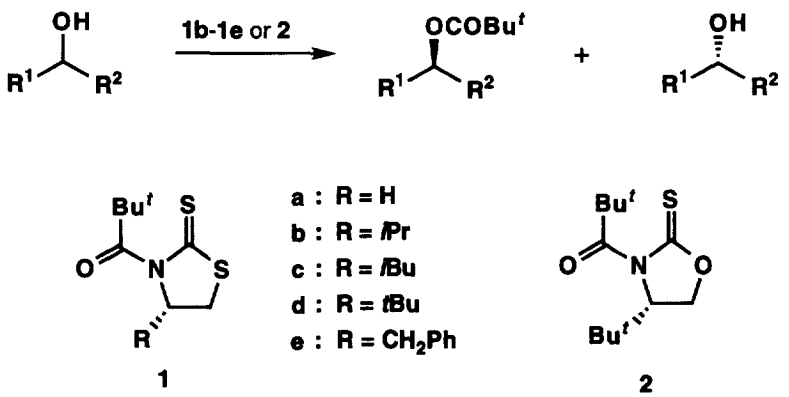
Abstract: Kinetic resolution of *sec*-alcohols was performed by using axially chiral twisted amides, 4-(*S*)-alkyl 3-pivaloyl-1,3-thiazolidine-2-thiones (**1b-1d** and **2**). The (*S*)-pivalates were selectively produced under neutral conditions; in contrast, the (*R*)-isomers were produced as major products in the presence of MeMgBr. Copyright © 1996 Elsevier Science Ltd

Kinetic resolution of racemic *sec*-alcohols by way of enzymatic acyl transfer reaction is an effective method for obtaining chiral alcohols and has been applied to organic syntheses.[1] However, relatively few studies on non-enzymatic approaches have been reported.[2,3]

We previously reported that the highly twisted amide **1a**[4] serves as a selective acylating agent for diols under neutral conditions.[5] Here we describe enantioselective acylation of *sec*-alcohols using chiral twisted amides **1b-1e** and **2** which possess axial chirality based on the C(O)-N bond rotation (Scheme 1). Although axially chiral imides and amides dependent on the C-N bond rotation have been employed in some asymmetric synthesis,[6] no axially chiral C(O)-N twisted amide has been known. Such an axially chiral twisted amide is postulated to be a transition intermediate of a peptide substrate during enzymatic hydrolysis.[7]

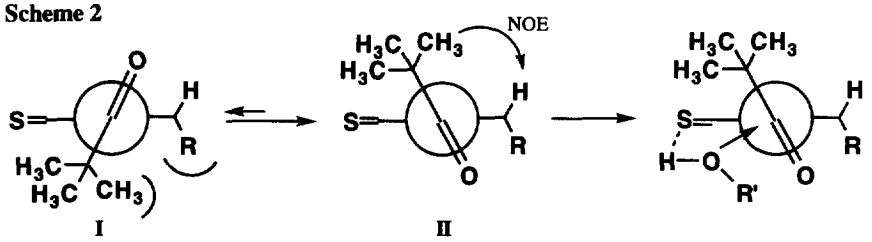
Scheme 1



As enantioselective acylating agents, we prepared (*S*)-4-alkyl 3-pivaloyl-1,3-thiazolidine-2-thiones **1b**, **1c**,[8] **1d**,[9] and **1e** and (*S*)-4-*tert*-butyl-3-pivaloyl-1,3-oxazolidine-2-thione (**2**) from the corresponding L-amino alcohols.[10] These amides exist overwhelmingly in the rotamer **II** in solution (Scheme 2), which was confirmed by NOE experiments between the *t*Bu and C4 methine protons.[11] The preference in the rotamer **II** will arise from the steric repulsion between the *t*Bu and C4 substituent groups. As a result, these amides have axial chirality around the C(O)-N bond as described in Scheme 2. The amides are also in equilibrium of *N*-pivaloyl and *S*-pivaloyl forms, and, except in **1d**, the former is largely predominant,[12] which was confirmed by ^{1}H, ^{13}C NMR and IR analysis.

Table 1 shows the results of the kinetic resolution of racemic *sec*-alcohols **3-8** with the amides **1b-1e** and **2**. The enantiomeric excess of the resulting esters was determined by HPLC analysis using a chiral column[13] after hydrolysis into the starting alcohol. Determination of the absolute configuration was performed by the comparison of the specific rotations of the hydrolyzed alcohols with those reported.[14] Entries 1-5 show the results of the acylation of 1-indanol (**3**) with the amide **1d** under neutral conditions in various solvents. Each reaction gave (*S*)-1-indanoyl pivalate as the major product. Among the various solvents employed, hexane was the most effective, whereas tetrahydrofuran was the least effective.

Scheme 2



In the reactions of 1-tetralol (**4**) with twisted amides, considerable differences in the selectivity were observed (entries 8-12). Thus, as the steric bulkiness of the C4 substituent groups increased, the selectivity also increased. Reducing the amount of 1-tetralol used from five to two equivalents resulted in a slight decrease in enantiomeric purity (entry 13). Addition of triethylamine enhanced the reaction rate sufficiently to proceed even at room temperature and to give the highest enantioselectivity (entries 14 and 15), though the reactivity of **2** was much lower than that of **1d**. From comparison of the selectivities in the acylation of cyclic alcohols **3-5** with **1d**, it is apparent that the ring size exerts a significant effect on the selectivity (entries 5, 10, and 16). On the other hand, the selectivities in the cases of acyclic alcohols **6-8** are almost similar (entries 17, 19 and 20).

Although the mechanism of the generation of the stereoselectivity is not clear, a plausible mechanism is that a *sec*-alcohol attacks the carbonyl carbon of the rotamer **II** from the less hindered side *via* a 6-membered transition structure as described in Scheme 2. The substituent groups at C4 may affect their C(O)-N twist angles, which influence the stability of the transition structures. Although the amide **1d** is mainly in S-pivaloyl form in solution, the reaction is considered to proceed from the *N*-pivaloyl form, because the selectivity is similar to that in the case of structurally analogous amide **2** which is mainly in *N*-pivaloyl form. Furthermore, the chiral center and the carbonyl group of the *S*-pivaloyl form are too apart from each other to discriminate the enantiomeric alcohols.

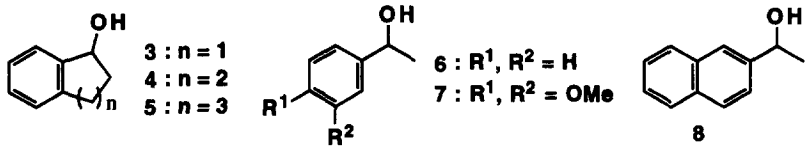


Table 1. Enantioselective pivaloylations of racemic *sec*-alcohols with twisted amides **1b-1e** and **2**.

Entry	Alcohol[a)]	Amide	Solv	Additives[b)]	Temp/°C	Time/h	Yield[c)]/%	ee/%	Config
1	**3**	**1d**	THF	-	reflux	71	72	26	*S*
2	**3**	**1d**	$CHCl_3$	-	reflux	15	89	35	*S*
3	**3**	**1d**	CH_3COOEt	-	reflux	23	94	36	*S*
4	**3**	**1d**	toluene	-	80	22	97	37	*S*
5	**3**	**1d**	hexane	-	reflux	22	92	49	*S*
6	**3**	**1d**	CH_2Cl_2	MeMgBr	0	2	49	19	*R*
7	**3**	**1b**	CH_2Cl_2	MeMgBr	0	4	74	39	*R*
8	**4**	**1b**	hexane	-	reflux	14	99	57	*S*
9	**4**	**1c**	hexane	-	reflux	15	98	38	*S*
10	**4**	**1d**	hexane	-	reflux	18	92	80	*S*
11	**4**	**1e**	hexane	-	reflux	15	97	44	*S*
12	**4**	**2**	hexane	-	reflux	14	91	75	*S*
13	**4**[d)]	**1d**	hexane	-	reflux	14	92	70	*S*
14	**4**	**1d**	hexane	Et_3N	r.t.	14	87	84	*S*
15	**4**	**2**	hexane	Et_3N	r.t.	6 days	93	79	*S*
16	**5**	**1d**	hexane	-	reflux	14	90	46	*S*
17	**6**	**1d**	hexane	-	reflux	28	94	45	*S*
18	**6**	**1d**	CH_2Cl_2	MeMgBr	0	6	53	42	*R*
19	**7**	**1d**	hexane	-	reflux	18	93	50	*S*
20	**8**	**1d**	hexane	-	reflux	12	98	56	*S*

a) Five eq. of alcohols were used unless otherwise noted. b) Five eq. of the additives were used.
c) Isolated yields. d) Two eq. of alcohol was used.

It is noteworthy that the addition of MeMgBr as a base reversed the stereoselectivity to yield the (*R*)-isomer predominantly (entries 6, 7 and 18). These results are related to the reported enantioselective

benzoylation of *sec*-alcohols with (*S*)-4-substituted 3-benzoyl-2-oxazolidinones in the presence of MeMgBr.[3,15] The reversal of the stereoselectivity may be attributed to the change in the transition conformations of the amides. Thus, the amides are mainly in highly twisted form **II** in the absence of MeMgBr, whereas in the presence of MeMgBr the conformation may change to the planar by chelating Mg^{2+} with both the carbonyl and thiocarbonyl groups. Such conformational differences will cause the opposite enantioselectivity.

In summary, rotation of the C(O)-N bond of the amides contributes not only to raise their reactivities toward alcohols but also to generate axial chirality which is responsible for discrimination of the enantiomeric alcohols *via* a proposed 6-membered transition structure as described in Scheme 2. Since an axially chiral twisted amide is postulated to be a transition intermediate of a peptide substrate during enzymatic hydrolysis,[7] these twisted amides are considered to be models of activated peptides.

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9. Synthesis of **1d**: To a solution of (*S*)-4-*tert*-butyl-1,3-thiazolidine-2-thione[16] (1.0 g, 5.7 mmol) and triethyl amine (1.0 g, 9.9 mmol) in CH_2Cl_2 (20 ml) was added dropwise pivaloyl chloride (752 mg, 6.27 mmol) at 0 °C and stirred for 4 h. The solution was washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give an oily product. This was dissolved in hexane and an insoluble solid was removed by filtration. The filtrate was recrystallizd from hexane to give white needles (1.08 g, 73 %). m.p. 78.5-79.5°C. IR (KBr) 1738, 1387, 1249, 1130, 1004 cm^{-1}; ^1H NMR ($CDCl_3$, TMS) δ 1.01 (s, 9 H), 1.28 (s, 9 H), 3.17 (t, *J* = 10.8 Hz, 1 H), 3.28(dd, *J* = 9.0, 10.8 Hz, 1 H), 4.15 (dd, *J* = 9.0, 10.8 Hz, 1 H); MS m/z 259 (M^+, 2), 118 (16), 85 (14), 57 (100).
10. The carbonyl stretching frequencies of **1b-1e** and **2** imply that their C(O)-N bonds are highly twisted, see ref. 8. The data obtained as KBr disc are as follows: **1b**: 1735 cm^{-1}; **1c**: 1720 cm^{-1}; **1d**: 1738 cm^{-1}; **1e**: 1721 cm^{-1}; **2**: 1737 cm^{-1}.
11. For example, 9% of NOE effect was observed for **1b**.
12. The ratios of *N*- to *S*-pivaloyl forms are as follows: **1b**, 6:1 (C_6D_6); **1c**, 11:1 ($CDCl_3$); **1e**, 10:1 ($CDCl_3$); **2**, 12:1 (C_6D_6); **1d**, 1: 25 ($C_6D_5CD_3$).
13. The analysis was carried out using a CHIRALCEL OB column with a 9:1 mixture of hexane and 2-propanol as an eluent solvent.
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15. 3-Acyl-2-oxazolidinones are much less reactive than 3-acyl-1,3-thiazolidine-2-thiones under neutral conditions, see ref 5.
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