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Studies Directed Toward the Design of Chiral Acylating Agents. The Utility of Chiral *N*-Benzoylimides in Enantioselective Alcohol Acylation

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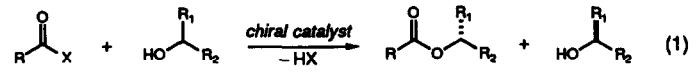
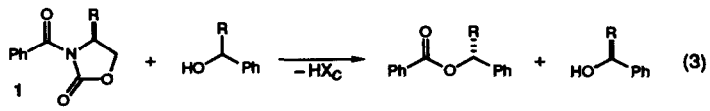
Abstract: *N*-benzoyl-4(*S*)-*tert*-butyl-2-oxazolidinone (**1b**) is found to be an efficient enantioselective acylating agent for aryl *n*-alkyl carbinols. Selective benzoylation of racemic aryl *n*-alkyl carbinols with kinetic selectivities of 20-30:1 for the (*R*) enantiomer is observed. The acylation process is promoted by formation of the derived magnesium alkoxides which may be accessed either from alcohol deprotonation with MeMgBr or through deprotonation with the Lewis acid-base combination of $MgBr_2/R_3N$.

Enzymatically mediated enantioselective acyl transfer processes are exceptionally effective in the kinetic resolution of racemic (eq 1) and *meso* secondary alcohols.[1] Such esterification processes are also of great value in the site-selective derivatization of polyhydroxylic compounds. At the present time, practical, nonenzymatic variants of these reactions do not exist. One of the long-term objectives of our laboratory is to develop such reactions. As an integral part of this program, we have also pursued the design of chiral acylating agents which might effect enantioselective delivery of conventional acyl residues (R = alkyl, aryl) to racemic 2° alcohols (eq 2).[2] In this instance, the chiral auxiliary must function as the leaving group while providing chiral recognition during the acyl transfer event.

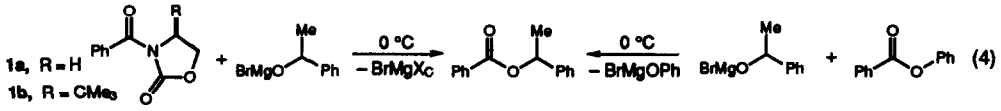


This letter describes preliminary results on the utility of *N*-benzoyloxazolidinones such as **1** in the enantioselective acylation[3] of racemic secondary alcohols (eq 3). We chose imide acylating agents such as **1** since we had indirect evidence that the rate (stereochemistry) determining step during acyl transfer between **1** and metal alkoxides was, in analogy with phenyl esters, associated with tetrahedral intermediate formation (*vide infra*).



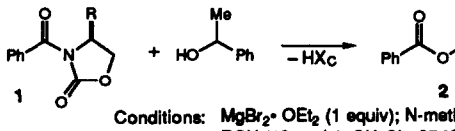
The Stereochemistry Determining Step. Prior studies from this laboratory have provided qualitative support for the assumption that *N*-acyl oxazolidinones may be classified as "active esters." For example, the base and hydroperoxide-mediated[4] hydrolysis of *N*-acyl oxazolidinones is considerably faster than structurally analogous alkyl carboxylic acid esters.[5] In a competitive transesterification experiment between phenyl benzoate and **1a** (1 equiv ROMgBr, 9 equiv ROH, 0 °C) we established that these two benzoylating agents acylate the

illustrated alkoxide at equivalent rates (eq 4). A similar competition experiment between **1a** and the *tert*-leucine derived oxazolidinone **1b**[6] revealed the apparent paradox that the more hindered analog was also the somewhat more reactive (k_{1b}/k_{1a} = 1.3) acylating agent (*vide infra*). This confirms that the kinetic behavior of acylating agents such as **1**,[7] is similar to the analogous hydrolysis (transesterification) kinetics of phenyl esters[8] where rate-determining attack of hydroxide ion at the acyl carbon dictates product composition. With the analogy between **1** and phenyl esters established, we investigated their potential as chiral acylating agents.



(4)

The Chiral Imide Auxiliary. In preliminary experiments designed to evaluate the effect of imide structure on enantiodiscrimination between α-methylbenzyl alcohol enantiomers, the illustrated imides **1b-1e** were treated with an excess (10 equiv)[9] of racemic alcohol and 1 equiv each of $MgBr_2$•OEt_2 and *N*-methylpiperidine (CH_2Cl_2, 25 °C), conditions which we speculated would provide access to the derived bromomagnesium alkoxide (eq 5).[10] In each of the indicated reactions employing the (*S*) *N*-benzoyl imides **1**, benzoylation was complete within 30 min (>90% isolated yield) with a stereoregular kinetic preference for esterification of the (*R*) alcohol enantiomer in each instance. In the illustrated series of acylations, there was a general correlation between the enantiomeric purity of the product benzoate[11] and the steric bulk of the R-substituent.



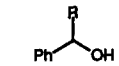
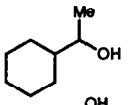
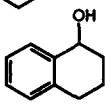
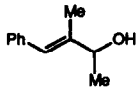
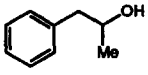
Conditions: $MgBr_2$• OEt_2 (1 equiv); N-methylpiperidine (1 equiv); ROH (10 equiv), CH_2Cl_2, 25 °C, 30 min.

Imide 1	% ee 2
1b, R = CMe_3	85 (*R*)
1c, R = $CHMe_2$	72 (*R*)
1d, R = c-C_6H_{11}	55 (*R*)
1e, R = CH_2Ph	57 (*R*)

(5)

Scope. The optimized reaction conditions for alcohol benzoylation with the (*S*)-*tert*-leucinol[12] derived imide **1b** included direct formation of the bromomagnesium alkoxide[13] of the indicated alcohols in the Table and temperature adjustment to 0 °C. Under these conditions, reaction times of 2-20 h afforded complete (>90%) reaction. Other counterions, solvents, and acyl residues[14] provided lower levels of acyl transfer selectivity.

Table I. Enantioselective Benzoylation of Representative Alcohols with Chiral Imide **1b**

entry	alcohol	time, h	ee, %[a]	entry	alcohol	time, h	ee, %[a]
				G		20	5
A	R = Me	2	95 (*R*)				
B	R = Et	2	90 (*R*)				
C	R = ^{n}Pr	18	93 (*R*)	H		8	53
D	R = ^{n}Bu	18	93 (*R*)				
E	R = ^{i}Pr	18	65 (*R*)				
F		20	85 (*R*)	I		4	15

Reaction Conditions: Imide **1b** (1.0 equiv) in anhydrous CH_2Cl_2 at 0 °C was added to a stirred ethereal solution of MeMgBr (1.1 equiv) and secondary alcohol (10 equiv) in CH_2Cl_2 (final concentration of **1b**, ~0.05 M). Conventional isolation and silica gel chromatography afforded isolated yields of >90% in all cases. [a] Enantiomeric purities of the saponified benzoate esters were determined by analysis of the derived Mosher's ester, except entry A which was carried out by chiral GLC using a Chiraldex® G-TA column.

From the data it appears that phenyl *n*-alkyl carbinols (entries A-D) form a homogeneous group of substrates which exhibit excellent enantioselectivities in the range 20-30:1 favoring preferential derivatization of the (*R*) alcohol enantiomer.[15] It is also evident that reaction selectivity is sensitive to the steric requirements of the alkyl group (entry E). The presence of an aryl moiety on the stereogenic center does not appear to be an absolute requirement for good asymmetric induction as entry F suggests; however, the aryl → cyclohexyl permutation effectively terminates chiral recognition (entry G). Finally, the constraints of ring formation on reaction enantioselectivity is documented (entry H).

Imide Structure. The greater reactivity of *N*-benzoyloxazolidinone **1b** relative to its unsubstituted counterpart **1a** led us to determine the X-ray structure of this imide (Figure 1).[16] As expected, the imide carbonyl groups are aligned in the expected *anti* orientation. In accommodating this geometry, resonance between the aryl group and the exocyclic carbonyl has been compromised.[17] Partial pyramidalization of the imide nitrogen, possibly a consequence of alleviated nonbonding interactions between the benzoyl and *tert*-butyl groups,[18] is even more interesting. This distortion from planarity renders the nitrogen stereogenic, enhances carbonyl reactivity, and presumably enforces the chiral environment in the vicinity of the exocyclic acyl carbon.

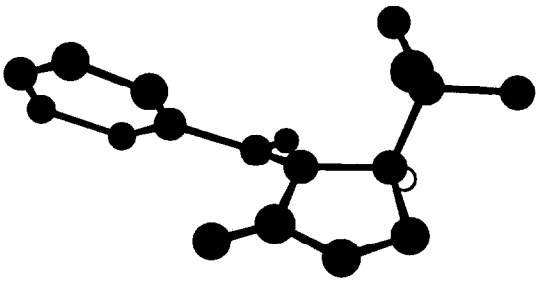


Figure 1. X-ray structure of imide **1b**.

At the present time we have not yet fully developed the scope of the chiral benzoylating agent **1b** nor are we in command of sufficient data to propose a self-consistent model for the observed enantioselective esterifications. Nevertheless, the reported cases provide sufficient precedent for the continued exploration of chiral imide acylating agents as valuable tools in stereoselective synthesis.

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References and Notes

† SERC-NATO Postdoctoral Fellow, United Kingdom, 1991-93.

1. (a) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114-120. (b) Chen, C-S.; Sih, C. J. *Angew. Chem. Int. Ed. Eng.* **1989**, *28*, 695-707. (c) Jones, J. B. *Tetrahedron*, **1986**, *42*, 3351-3403. (d) Whitesides, G. M.; Wong, C.-H. *Angew. Chem. Int. Ed. Eng.* **1985**, *24*, 617-638.
2. This is a related strategy to that employed by Horeau, see: Weidman, R.; Horeau, A. *Bull. Soc. Chim. Fr.* **1967**, 117-124 and references cited therein.
3. Diacylimides and their sulfur counterparts are well known as effective acylating agents. For several recent studies see: (a) Kikugawa, Y.; Mitsui, K.; Sakamoto, T.; Kawase, M.; Tamiya, H. *Tetrahedron Lett.* **1990**, *31*, 243-246. (b) Yamada, S. *J. Org. Chem.* **1992**, *57*, 1591-1592. (c) Yamada, S. *Tetrahedron Lett.* **1992**, *33*, 2171-2174.
4. Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141-6144.
5. Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063-1072. See the transformation of **9** → **14** (Scheme III) in this study.

6. (4*S*)-*tert*-butyl-2-oxazolidinone (3) was prepared from (*S*)-*tert*-leucinol (Ref 12) according to the general procedure reported by us (Gage, J. R.; Evans, D. A. *Organic Syntheses*, **1989**, *68*, 77-82) in a yield of 88%: mp 105.8-106.4 °C. The *N*-benzoylation of 3 to afford **1b** was carried out in analogy to a related acylation (Gage, J. R.; Evans, D. A. *ibid*, **1989**, *68*, 83-91) in 85% yield: mp 130 °C; $[\alpha]_D$ +203.2 ° (*c* 1.00, $CHCl_3$); IR (solution in CCl_4) 3026, 2968, 1781, 1688, 1488, 1450, 1385, 1370, 1329, 1220, 1212, 1210, 1188, 1100, 1069 cm^{-1}; ^1H NMR ($CDCL_3$, 300 MHz) δ 7.72 (dd, 2 H, J = 6.6, 1.5 Hz, *o*-Ar), 7.54 (t, 1 H, J = 7.1 Hz, *p*-Ar), 7.41 (t, 2 H, J = 7.7 Hz, *m*-Ar), 4.74 (dd, 1 H, J = 6.9, 4.1 Hz, C_4-H), 4.35 (t, 2 H, J = 3.5 Hz, C_5-H), 1.00 (s, 9 H, ^{t}Bu); ^{13}C NMR ($CDCL_3$, 100.6 MHz) δ 170.4, 154.0, 133.0, 132.8, 129.7, 127.9, 64.9, 60.6, 36.0, 25.4; Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.95; H, 7.02; N, 5.56.
7. This reactivity trend is consistent with the pKa comparison between the 2-oxazolidinone moiety (pKa 20.5/DMSO) and phenol (pKa 18/DMSO) which provides a qualitative measure of leaving group potential of the indicated acyl substituent. These measurements have been carried out by F. G. Bordwell. For a general tabulation of acidity data in DMSO see: Bordwell, F. G. *Accounts Chem. Res.* **1988**, *21*, 456-463. The fact that 4-benzyl-2-oxazolidone is *ca.* 4 pKa units *more* acidic than related noncyclic amides and urethanes may be attributed to the same effects which have been identified in enhancing the C–H acidity of lactones over related ester substrates. For a discussion of this issue see: Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1988**, *110*, 1872-1874.
8. Jencks, P. W.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622-2637.
9. With 2 equiv of racemic alcohol, the reaction of **1b** under identical conditions proceeds to ~80% conversion after 24 h; however, formation of the bromomagnesium alkoxide with MeMgBr (*vide infra*), in the presence of 1 equiv of tetramethylethylenediamine affords complete reaction with **1b** in 1 h at 0°C providing the (*R*) benzoate in 49% ee.
10. Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622-2624.
11. The optical rotation of **2**: $[\alpha]_D$ +28.8 ° (*c* 0.89, $CHCl_3$).
12. McKenron, M.J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568-3571.
13. The use of the Grignard reagent, rather than $MgBr_2$•OEt_2/*N*-methylpiperidine to form the magnesium alkoxides afforded slightly higher acyl transfer enantioselectivities.
14. Except for the *N*-β-naphthoyl imide which afforded comparable selectivities to the benzoyl residues in these acyl transfer reactions.
15. Absolute configurational assignments of the benzoates described in entries A-F were made via their derived 2° alcohols. See Janssen, A. J. M.; Klunder, A. J. H.; Zwannenburg, B. *Tetrahedron*, **1991**, *47*, 7645-7662 and references cited therein. These assignments were confirmed by the recently published NMR method for the assignment of absolute configuration of secondary alcohols: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.
16. The authors wish to thank M. J. Scott and A. R. Muci for carrying out the X-ray analysis.
17. The dihedral angle between the aryl and C=O substituents is 37.7°.
18. We have obtained numerous X-ray structures of 4-benzyl- and isopropyl-substituted *N*-acyloxazolidinones. This is the first instance where a deviation from planarity of the imide nitrogen has been observed.

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