Kinetic Resolution of Arylalkylcarbinols Catalyzed by a Planar-Chiral Derivative of DMAP: A New Benchmark for Nonenzymatic Acylation

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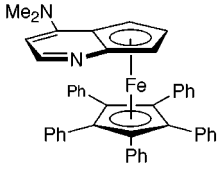
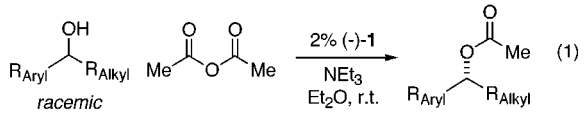
The kinetic resolution of alcohols by nonenzymatic acylation catalysts has been the focus of intense interest, and within the past 2 years the first catalysts have been described that provide useful levels of selectivity (s = selectivity factor ≥ 10).[1,2] Members of three families of secondary alcohols—arylalkylcarbinols,[3−5] cycloalkanols,[4,6] and allylic alcohols[5]—have now been resolved with good to excellent enantioselection. For the kinetic resolution of arylalkylcarbinols, the most effective and the most versatile acylation catalyst reported to date is planar-chiral DMAP derivative **1** (s = 12−52; eq 1).[5] In this paper, we describe

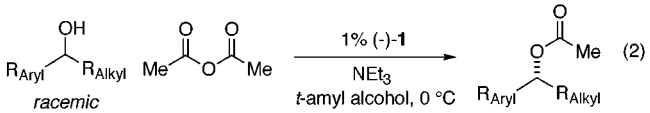


(-)-**1**

modified reaction conditions under which catalyst **1** displays greatly enhanced enantioselectivity, thereby establishing a new benchmark for kinetic resolutions of arylalkylcarbinols (s = 32−95; eq 2); furthermore, we apply this system for the first time to racemic and meso diols.

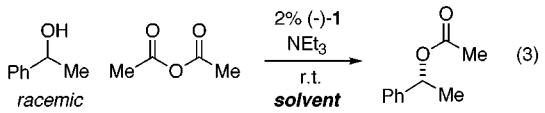


***s* = selectivity factor = 12 to 52**



***s* = 32 to 95**

A wide-ranging solvent study established that both the rate and the enantioselectivity of the acylation of (±)-1-phenylethanol are highly dependent on solvent (eq 3). Although we have not yet been able to correlate stereoselectivity with any single solvent parameter, it is clear that *tert*-amyl alcohol is the solvent of choice for acylations catalyzed by **1**. Interestingly, *tert*-amyl alcohol itself is not acylated to any significant extent under these conditions.



solvent	% conversion after 1.0 h	s
DMF	6	3.4
CH_3CN	10	3.6
CH_2Cl_2	14	7.0
acetone	8	8.7
THF	4	9.6
EtOAc	6	11
toluene	13	11
Et_2O	8	13
t-amyl alcohol	36	27

The enhanced rate of acylation in *tert*-amyl alcohol, relative to the Et_2O that was used in our previous study, has important practical consequences. We had determined earlier that the selectivity in kinetic resolutions catalyzed by **1** is temperature dependent, with higher selectivity observed at lower temperature. Unfortunately, acylations using 2% catalyst in Et_2O at 0 °C are too slow to be convenient (several days), thereby precluding exploitation of this temperature effect. On the other hand, we have established that acylations in *tert*-amyl alcohol proceed at a convenient rate at 0 °C, even using only 1% catalyst (typically <24 h), and we have observed a marked improvement in the selectivity factor under these conditions (27 → 43 for (±)-1-phenylethanol). *Thus, the net effect of these studies is a tripling of selectivity (13 → 43) with one-half of the previous catalyst loading.*

As is evident in Table 1, this substantial increase in selectivity when kinetic resolutions with catalyst **1** are conducted in *tert*-amyl alcohol at 0 °C has proved to be general. As a point of reference, for selectivity factors greater than 49, unreacted alcohol of greater than 99% ee is obtained at less than 55% conversion. These kinetic resolutions are not sensitive to small amounts of oxygen, moisture, or adventitious impurities—reactions run exposed to air with unpurified reagents provide selectivities identical to those observed for reactions run under an inert atmosphere with purified reagents. To date, other nonenzymatic acylation catalysts have been effective (s ≥ 10) for the kinetic resolution of only two arylalkylcarbinols—phenyl-*tert*-butylcarbinol (s = 12−15;[3] cf. entry 2) and *o*-tolylmethylcarbinol (s = 12;[4] cf. entry 5).

(1) Selectivity factor = [(rate of fast-reacting enantiomer)/(rate of slow-reacting enantiomer)]. For a review of kinetic resolution, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330.

(2) For reviews of enantioselective acylation of alcohols by enzymes, see: (a) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*; VCH: New York, 1995. (b) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: New York, 1994; Chapter 2. (c) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114−120. (d) Sih, C. J.; Wu, S.-H. *Top. Stereochem.* **1989**, *19*, 63−125.

(3) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430−431.

(4) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543−8546.

(5) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492−1493.

(6) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169−3170.

(7) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584−2585.

(8) Procedure for a preparative-scale reaction (eq 4): *o*-Tolylmethylcarbinol (1.11 g, 8.14 mmol), *tert*-amyl alcohol (16 mL), and triethylamine (0.67 mL, 4.8 mmol) were added to a flask containing (−)-**1** (27.7 mg, 0.0419 mmol). After gentle heating to dissolve the catalyst, the reaction mixture was cooled in an ice bath, and acetic anhydride (0.46 mL, 4.9 mmol) was added by syringe. After 25.5 h, the reaction was quenched with MeOH (5 mL). The mixture was passed through a short plug of silica (50% → 100% EtOAc/hexanes, then 10% NEt_3/EtOAc) to separate the alcohol and the acetate from the catalyst. The solution of alcohol and acetate was concentrated, and the resulting oil was purified by flash chromatography (5% → 25% Et_2O/pentane), which provided 639 mg of acetate and 517 mg of alcohol. GC analysis of the alcohol revealed a 93% ee of the *S* enantiomer. A sample of the acetate was reduced with $LiAlH_4$ to the alcohol, which GC analysis revealed to be the *R* enantiomer in 90% ee.

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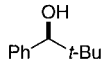
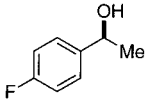
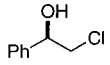
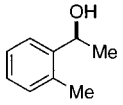
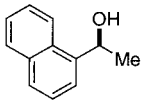
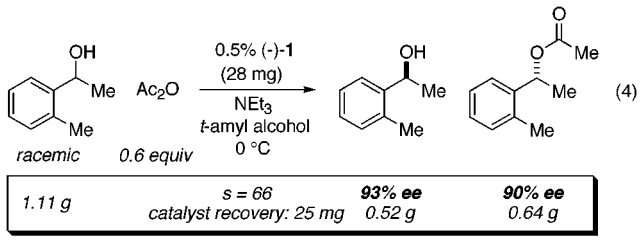
Table 1. Kinetic Resolution of Arylalkylcarbinols Catalyzed by (−)-1

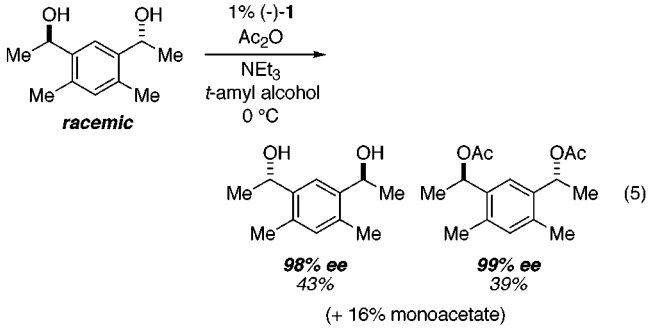
entry	unreacted alcohol, major enantiomer	s (selectivity factor)[a] Et_2O 2% catalyst r.t.	s (selectivity factor)[a] *t*-amyl alcohol 1% catalyst 0 °C
1		14	**43** *99% ee @ 55% conv.*
2		52	**95** *96% ee @ 51% conv.*
3		18	**68** *99% ee @ 54% conv.*
4		12	**32** *98% ee @ 56% conv.*
5		22	**71** *99% ee @ 53% conv.*
6		22	**65** *95% ee @ 52% conv.*

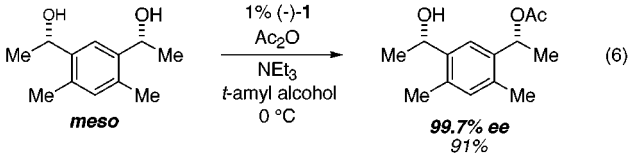
[a] The selectivity factors are averages of two or more runs. The ee data are for specific runs.

With such high selectivity factors, it is now possible to obtain both alcohol *and* acetate in excellent ee without relying upon more complicated strategies such as parallel kinetic resolution.[7] Thus, the preparative-scale reaction illustrated in eq 4 provides *o*-tolylmethylcarbinol and its acetylated derivative in >90% ee.[8] The catalyst loading in this kinetic resolution is low (0.5%), and the catalyst recovery is high (89%).



To date, there have been no reports of highly effective asymmetric acylation of a diol by a nonenzymatic catalyst.[9] We have now established that **1** can efficiently kinetically resolve a racemic diol as well as desymmetrize a meso diol. In the case of the racemic diol, the cumulative effect of two sequential enantioselective processes affords both diol and diacetate in very high ee (≥98% ee; eq 5). In the case of the meso diol, the high stereoselectivity of catalyst **1** provides the desymmetrized monoacetate in excellent ee and high yield (eq 6).[10]





In conclusion, we have demonstrated that planar-chiral DMAP derivative **1** catalyzes the kinetic resolution of arylalkylcarbinols with remarkable efficiency. Interestingly, the optimum solvent for this process is a tertiary alcohol, *tert*-amyl alcohol. *Our results define a new benchmark for the nonenzymatic asymmetric acylation of arylalkylcarbinols,* both in terms of scope and of enantioselectivity. Significant from a practical point of view are the high catalyst turnover and the catalyst recoverability, as well as the low sensitivity of the reaction to oxygen, moisture, and adventitious impurities.

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Supporting Information Available: Experimental procedures and compound characterization data (25 pages).

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(9) The best selectivity reported to date is for the acylation of *meso*-hydrobenzoin (product of 68% ee at 84% conversion; ref 3).

(10) (a) For a discussion and leading references, see: Kroutil, W.; Kleewein, A.; Faber, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3251−3261, 3263−3274. (b) Guo, Z.-W.; Wu, S.-H.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 4942−4945. (c) Reference 1.