Effective Kinetic Resolution of Secondary Alcohols with a Planar−Chiral Analogue of 4-(Dimethylamino)pyridine. Use of the Fe(C_5Ph_5) Group in Asymmetric Catalysis

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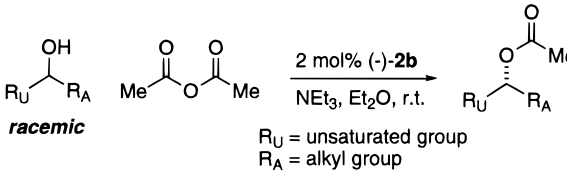
We recently reported that planar−chiral π-complexes of heterocycles with transition metals (e.g., **1** and **2a**, Figure 1) serve as effective nucleophilic catalysts for an array of useful processes, including the acylation of alcohols with diketene and the addition of Et_3SiCN to aldehydes.[1] Furthermore, we established that enantiopure azaferrocene derivative **1** effects the kinetic resolution[2] of secondary alcohols (acylation with diketene) with good enantioselectivity. In this paper, we describe a second-generation system for kinetic resolution that employs 2 mol % of iron complex **2b** as the chiral catalyst and inexpensive acetic anhydride as the acylating agent (eq 1). This process represents a significant advance in the state-of-the-art for enantioselective acylation of alcohols using nonenzymatic chiral catalysts.[3−5]



(1)

Although the preliminary results that we had obtained for the kinetic resolution of secondary alcohols with enantiopure azaferrocene derivative **1** were quite promising, the superior activity of 4-(dimethylamino)pyridine (DMAP) analogue **2a**[1] provided a powerful incentive to also explore its effectiveness as a chiral catalyst. Unfortunately, we observed no enantioselectivity when racemic 1-phenylethanol was treated with diketene in the presence of 2 mol % of complex (−)-**2a** (eq 2). An analogous reaction using acetic anhydride as the acylating agent[6] also proved disappointing ($s = 1.7$).

We therefore turned our attention to modifying catalyst **2a** to afford a more asymmetric environment in the vicinity of the nucleophilic nitrogen atom. Increasing the steric bulk of the metal fragment or of the 7-position of the pyrindinyl ring system appeared to be reasonable strategies, and we focused our initial efforts on the latter approach. We discovered, however, that

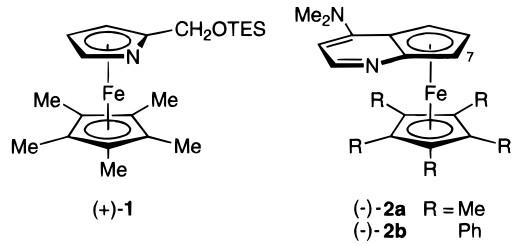
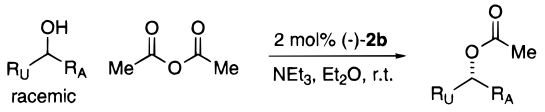


Figure 1. Planar−chiral nucleophilic catalysts.

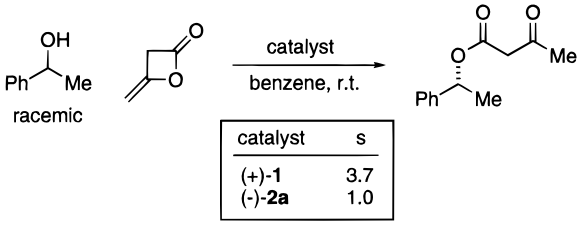
Table 1. Catalytic Enantioselective Acylation of Chiral Secondary Alcohols



entry	unreacted alcohol, major enantiomer	% ee of unreacted alcohol (% conversion)	s[a] (selectivity)
1	OH, Ph, R = Me	95.2 (62)	14
2	OH, Ph, R = Et	98.8 (62)	20
3	OH, Ph, R = *i*-Pr	97.7 (55)	36
4	OH, Ph, R = *t*-Bu	92.2 (51)	52
5	OH, Ph, R = CH_2Cl	98.9 (69)	12
6	OH, Me, X = F	99.2 (64)	18
7	OH, Me, X = OMe	94.5 (60)	15
8	OH, Me	99.7 (63)	22
9	OH, Ph, Me	99.1 (67)	14
10	OH, Ph, Me, Me	99.0 (61)	22

[a] For each substrate, comparable selectivities (s) are observed at low (2−10%) and at high (51−69%) conversion.

complexes derived from incorporation of a methyl or a trimethylsilyl substituent at the 7-position of **2a** are poor catalysts for alcohol acylation, and they provide little or no enantioselectivity in the kinetic resolution of (±)-1-phenylethanol.



(2)

We next explored the possibility of improving the selectivity by increasing the steric bulk of the metal fragment, an approach that proved fruitful. Thus, replacement of the η^5-C_5Me_5 group of **2a** with η^5-C_5Ph_5[7,8] affords complex **2b**, which serves as a highly enantioselective catalyst for the kinetic resolution of an

(1) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230−7231.
(2) For a review of kinetic resolution, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330.
(3) For previous reports, see: (a) Wegler, R. *Liebigs Ann. Chem.* **1932**, *498*, 62−76. (b) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430−431. (c) Reference 1.
(4) For reports of highly enantioselective acylation with a stoichiometric chiral acylating agent, see: (a) Evans, D. A.; Anderson, J. C.; Taylor, M. K. *Tetrahedron Lett.* **1993**, *34*, 5563−5566. (b) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809−1810.
(5) For reviews of enantioselective acylation of alcohols by enzymes, see: (a) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: New York, 1994; Chapter 2. (b) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114−120. (c) Sih, C. J.; Wu, S.-H. *Top. Stereochem.* **1989**, *19*, 63−125.
(6) Complex **1** is not an effective catalyst for the acylation of 1-phenylethanol by acetic anhydride.
(7) C_5Ph_5H is available from Aldrich. For an inexpensive synthesis of C_5Ph_5H, see: Dyumaev, V. K.; Davydov, D. V.; Beletskaya, I. P. *Russ. Chem. Bull.* **1993**, *42*, 571−573.
(8) (a) For the first synthesis of an (η^5-C_5Ph_5)Fe complex, see: McVey, S.; Pauson, P. L. *J. Chem. Soc.* **1965**, 4312−4318. (b) For a review of the use of "supracyclopentadienyl" ligands in organometallic chemistry, see: Janiak, C.; Schumann, H. *Adv. Organomet. Chem.* **1991**, *33*, 291−393.

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array of unsaturated alcohols (Table 1). In the presence of 2 mol % of (−)-**2b**,[9] enantiomeric alcohols react with acetic anhydride (Et_2O, room temperature) at relative rates ranging from 12−52 to 1.[10,11] For arylalkyl carbinols, selectivity is a strong function of the size of the alkyl group (entries 1−4) but not of the electronic nature of the aromatic ring (entries 1, 6, and 7). Not only arylalkyl carbinols (entries 1−8) but also allylic alcohols can be resolved with synthetically useful levels of stereoselectivity (entries 9 and 10). With the single exception of phenyl-*tert*-butyl carbinol (entry 4), for which a selectivity factor of 15 has been reported,[3b] none of the substrates depicted in Table 1 had previously been resolved with a selectivity factor greater than 7 in the presence of a nonenzymatic chiral acylation catalyst.[3]

These kinetic resolutions are operationally straightforward to conduct,[12] since catalyst **2b** is stable to oxygen and to moisture, both as a solid and in solution. Indeed, when the acylations are run under air with unpurified reagents, essentially identical selectivities are observed as when the reactions are run under nitrogen with purified reagents. Finally, the catalyst can be recovered quantitatively (>98%) at the end of the reactions.

In conclusion, we have established that planar−chiral DMAP analogue **2b** serves as an effective catalyst for the kinetic resolution of racemic secondary alcohols. The enantioselectivities that we have observed are substantially better than for any previously reported nonenzymatic asymmetric acylation catalyst. It is important to note that the stereoselectivity displayed by complex **2b** is attributable in large part to the η^5-C_5Ph_5 group. Although the ferrocene framework is a common component of chiral catalysts,[13] to the best of our knowledge this is the first study that demonstrates that an increase in the steric bulk of a remote cyclopentadienyl ring can lead to a significant improvement in enantioselectivity.[14] Ongoing efforts are focused on extending this observation to other systems and on developing additional applications of **2b** and related complexes in asymmetric catalysis.

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Supporting Information Available: Experimental procedures and compound characterization data (14 pages). See any current masthead page for ordering and Internet access instructions.

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(9) The absolute configuration of (−)-**2b** has been tentatively assigned on the basis of an X-ray crystallographic study (anomalous dispersion). Ruble, J. C.; Hoic, D. A. Unpublished results.

(10) Optimization studies (kinetic resolution of (±)-1-phenylethanol) revealed the following: (1) Higher stereoselectivity is observed with acetic anhydride than with diketene, benzoic anhydride, methacrylic anhydride, etc. (2) Higher stereoselectivity and lower rates are observed at lower temperature. (3) Comparable stereoselectivity is observed in Et_2O, toluene, and CH_2Cl_2.

(11) For the reactions illustrated in Table 1, the enantiomeric excess of the acylated alcohol ranges from 44 to 88%.

(12) Procedure for preparative-scale reaction: Catalyst (−)-**2b** (44.5 mg, 0.0674 mmol, 2 mol %), (±)-1-phenylethanol (412 mg, 3.37 mmol), Et_2O (6.75 mL), NEt_3 (0.352 mL, 2.53 mmol), and acetic anhydride (0.239 mL, 2.53 mmol) were added in turn to a 25 mL round-bottom flask, providing a dark-purple solution. After 78 h of stirring at room temperature, this reaction mixture was filtered through a short plug of silica gel (50% → 75% EtOAc/hexane as the eluant) in order to remove the catalyst. Analysis of the resulting solution by GC (Chiraldex B-PH) revealed a 57.3% ee of (*R*)-acetate and a 97.3% ee of (*S*)-alcohol, indicating a selectivity (*s*) of 14.7 at 63% conversion. Flash chromatography (5% → 25% Et_2O/pentane) afforded 142 mg (34%, based on starting alcohol) of (*S*)-1-phenylethanol (97.3% ee).

(13) (a) *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: New York, 1995. (b) Togni, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475−1477.

(14) *Decreased* enantioselectivity upon substitution of an η^5-C_5H_5 group with a more bulky η^5-C_5Me_5 group has been reported: Abbenhuis, H. C. L.; Burckhardt, U.; Gramlich, V.; Martelletti, A.; Spencer, J.; Steiner, I.; Togni, A. *Organometallics* **1996**, *15*, 1614−1621.