Nonenzymatic Kinetic Resolution of Propargylic Alcohols by a Planar−Chiral DMAP Derivative: Crystallographic Characterization of the Acylated Catalyst

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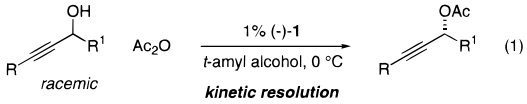
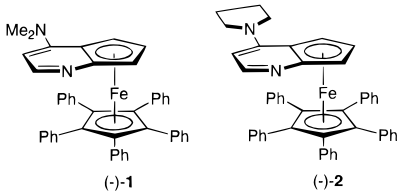
Significant progress has recently been made in the development of nonenzymatic acylation catalysts for the kinetic resolution of secondary alcohols. Whereas prior to 1996, no such catalysts afforded a selectivity factor (*s*) of 10 or larger,[2] since that time several quite different catalysts have been described that provide useful levels of enantioselection. To date, members of three families of alcohols—aryl alkyl carbinols,[3−5] cycloalkanols,[4−7] and allylic alcohols[5]—have been kinetically resolved with good to outstanding stereoselectivity. In this paper, we report that members of a fourth family of alcohols, propargylic alcohols,[8] can be resolved with a planar−chiral catalyst derived from DMAP (eq 1), and we present a structural investigation of the acetylated catalyst.



(1)

In early studies we established that planar−chiral DMAP derivative **1** is superior to PPY derivative **2** in catalyzing the



kinetic resolution of 4-phenyl-3-butyn-2-ol (eq 2; *s* = selectivity factor). In contrast to our previous work with aryl alkyl carbinols,[5] we found that with propargylic alcohols, NEt_3 itself catalyzes the acylation process to an appreciable extent. To minimize this nonselective background reaction, we explored the replacement of NEt_3 with a variety of other Brønsted bases, both organic and inorganic; ultimately, however, we discovered that the highest enantioselection is achieved when no base is added (Table 1).[9] A survey of acylating agents revealed that acetic anhydride affords the best selectivity among the anhydrides that we have investigated (Table 2, entry 1). In the presence of more bulky alkyl anhydrides (entries 2 and 3) or of an aromatic anhydride (entry 4), we observe diminished *s* values.

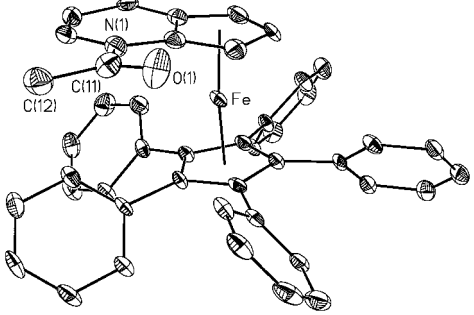
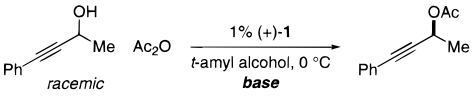


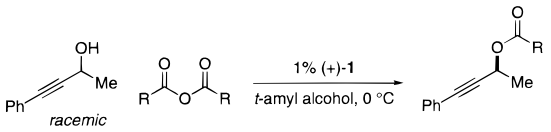
Figure 1. ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level, of acetylated **1**. The SbF_6 counterion and two solvent molecules (THF) have been omitted for clarity.

Table 1. Selectivity Factor as a Function of Base

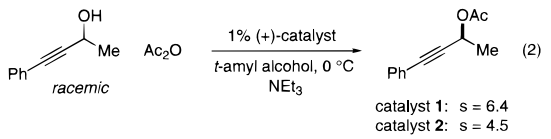


entry	base	*s*
1	NEt_3	6.4
2	$N(i\text{-}Pr)_2Et$	12
3	2,6-lutidine	13
4	$NaHCO_3$	13
5	none	17

Table 2. Selectivity Factor as a Function of Anhydride



entry	R	*s*
1	Me	17
2	*n*-Pr	14
3	*i*-Pr	7.0
4	Ph	2.0



(2)

An array of propargylic alcohols can be resolved with useful levels of stereoselection using this acylation system (Table 3).[10,11]

(1) Correspondence concerning the X-ray crystallograpy should be directed to D.A.H.

(2) 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.

(3) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430−431. See also: Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809−1810 and Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584−2585.

(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. (b) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794−2795. (c) Garrett, C. E.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 7479−7483.

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

(7) (a) Miller, S. J.; Copeland, G. T.; Papaiannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *110*, 1629−1630. (b) Copeland, G. T.; Jarvo, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784−6785.

(8) For leading references to methods for preparing optically active propargylic alcohols, see: Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739.

(9) In the absence of NEt_3, the rate of acylation decreases, due to protonation of the catalyst by acetic acid.

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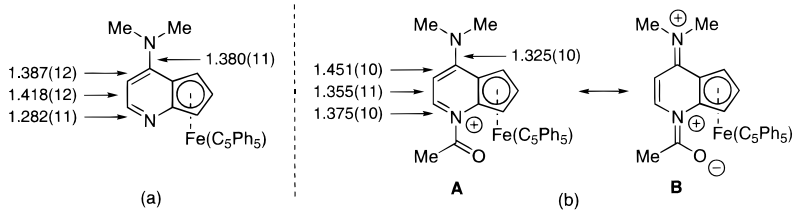
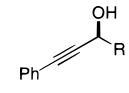
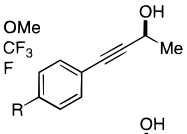
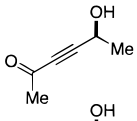
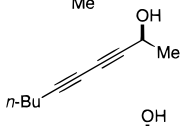
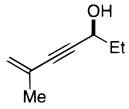


Figure 2. Bond distances (Å) for the (dimethylamino)pyridine fragment of (a) complex **1**; (b) acetylated complex **1**.

Table 3. Kinetic Resolutions of Propargylic Alcohols by 1% (−)-**1**

entry		unreacted alcohol, major enantiomer	selectivity factor [a] (ee of unreacted alcohol)
1	R = Me		***20*** *(96% ee @ 58% conv.)*
2	Et		***18*** *(94% ee @ 58% conv.)*
3	*i*-Pr		***11*** *(93% ee @ 63% conv.)*
4	*t*-Bu		***3.8*** *(95% ee @ 86% conv.)*
5	R = OMe		***14*** *(94% ee @ 60% conv.)*
6	CF_3		***10*** *(99% ee @ 71% conv.)*
7	F		***13*** *(97% ee @ 65% conv.)*
8			***12*** *(95% ee @ 64% conv.)*
9			***10*** *(95% ee @ 66% conv.)*
10			***7.9*** *(94% ee @ 69% conv.)*

[a] The selectivity factors are averages of two runs.

In contrast to aryl alkyl carbinols, for which the selectivity factor *increases* as the steric demand of the alkyl group increases,[5a,b] for propargylic alcohols the selectivity factor *decreases* as the steric demand increases (entries 1−4). Interestingly, substitutions at positions far removed from the hydroxyl group can affect enantioselection (entry 1 vs entries 5−7). Kinetic resolutions of propargylic alcohols by catalyst **1** are more efficient when the remote position of the alkyne is substituted with an unsaturated group (e.g., aryl, carbonyl, alkynyl, alkenyl), rather than with an alkyl group (selectivity factor for (±)-3-octyn-2-ol: 3.9).

We have begun to pursue mechanistic studies of acylations catalyzed by planar−chiral DMAP derivative **1**. For reactions catalyzed by DMAP itself, an acylpyridinium salt is believed to be the active acylating agent.[12,13] Unfortunately, for catalyst **1** as for DMAP, the equilibrium for a mixture of catalyst and Ac_2O (1:1) strongly favors the starting materials.[12] On the other hand, use of a more reactive acylating agent such as AcCl leads to quantitative formation of the acylpyridinium salt. Disappointingly, we were not able to obtain X-ray quality crystals of this salt. However, exchange of chloride for SbF_6 (through treatment with $AgSbF_6$) afforded a new acylpyridinium salt that proved to be amenable to crystallization (Figure 1). To the best of our knowledge, this is the first structural characterization of the acylated form of a chiral, nonenzymatic acylation catalyst.[14]

The NMe_2 group, the pyridine ring, and the acetyl group of the acylpyridinium ion lie approximately in a single plane, a conformation consistent with extended conjugation (Figure 1). The changes in bond lengths of the (dimethylamino)pyridine fragment that are observed upon acylation are consistent with a substantial contribution by resonance structure **B** (Figure 2). Further support for significant conjugation is provided by the increased rotational barrier about the Me_2N-C bond in the acetylated catalyst ($\Delta G^{\ddagger} > 21$ kcal/mol) as compared to the parent compound ($\Delta G^{\ddagger} \approx 10$ kcal/mol).

Of the two possible rotamers of the acetyl group (about the N(1)−C(11) bond, Figure 1), the one observed in the crystal structure is consistent with minimization of steric interactions with the fused five-membered ring (the oxygen of the acetyl is smaller than the methyl).[15] Finally, it is interesting to note that the two cyclopentadienyl rings deviate from coplanarity by about 8°, perhaps due to repulsion between the pyridine ring and the phenyl substituents of the C_5Ph_5 group; of course, sterically blocking one face of the pyridine ring in an effective fashion is critical to the asymmetry of these planar−chiral catalysts.[16]

In summary, we have described the first effective nonenzymatic acylation catalyst for the kinetic resolution of propargylic alcohols. This report thus adds a new family of substrates to the three families that have previously been shown to be amenable to kinetic resolutions of this type. In addition, we have provided structural data regarding the acetylated form of catalyst **1**, which is likely a key intermediate in kinetic resolutions catalyzed by **1**. Future efforts will include studies directed at elucidating the origin of enantioselectivity in these acylation processes.

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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystallographic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Sample experimental: A vial containing 4-phenyl-3-butyn-2-ol (73.0 mg, 0.500 mmol) and catalyst (−)-**1** (3.3 mg, 0.0050 mmol) in *tert*-amyl alcohol (1.0 mL) was capped with a septum and sonicated to help dissolve the catalyst. The resulting purple solution was cooled to 0 °C, and Ac_2O (35.4 μL, 0.375 mmol) was added by syringe. After 49 h, the reaction was quenched by the addition of a large excess of MeOH. The acetate was then separated from the alcohol by column chromatography (10% → 50% EtOAc/hexanes; the catalyst can be recovered by adding NEt_3 to the eluant). Analysis of the acetate by chiral GC revealed a 68.6% ee of the *R* enantiomer. The alcohol was converted into the acetate and then analyzed by chiral GC, which revealed a 96.0% ee of the *S* enantiomer. These ee values correspond to a selectivity factor of 20.2 at 58.3% conversion.

(11) Notes: (a) The difference in selectivity factors that we report for the kinetic resolution of 4-phenyl-3-butyn-2-ol (Table 1, entry 5 and Table 2, entry 1: $s = 17$; Table 3, entry 1: $s = 20$) is due to a difference in the concentrations at which the reactions were run (1.0 vs 0.5 M in 4-phenyl-3-butyn-2-ol). (b) These reactions 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. The catalyst can be recovered in nearly quantitative yield at the end of the reaction. (c) We observed lower selectivity when the kinetic resolutions were run in other solvents.

(12) For reviews of the chemistry of DMAP, see: (a) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129−161. (b) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069−2076. (c) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583.

(13) For a crystal structure of acetylated DMAP, see: Jones, P. G.; Linoh, K.; Blaschette, A. *Z. Naturforsch.* **1990**, *45b*, 267−270.

(14) The SbF_6 acylpyridinium salt ($s = 2.5$) and the corresponding planar−chiral DMAP catalyst ($s = 2.1$) preferentially acylate the same enantiomer of 4-phenyl-3-butyn-2−ol (CH_2Cl_2, NEt_3, rt; the comparison could not be conducted in *tert*-amyl alcohol due to the insolubility of the SbF_6 salt).

(15) NMR studies (presaturation difference NOE experiments in CD_2Cl_2) indicate that this rotamer is also the only detectable rotamer in solution.

(16) For *non*acylated catalyst **1**, the cyclopentadienyl rings deviate from coplanarity by 10°; for the C_5Me_5 analogue of catalyst **1**, which provides significantly lower selectivity factors in kinetic resolutions, the corresponding angle is 2°.