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Desymmetrization of Meso 1,3- and 1,4-Diols with a Dinuclear Zinc Asymmetric Catalyst

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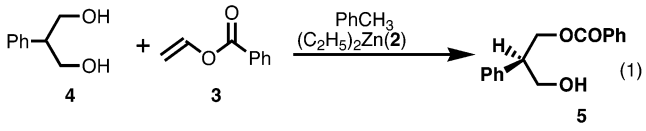
The use of nonenzymatic catalysts for asymmetric acylations of racemic alcohols, that is, kinetic resolutions, using chiral nucleophilic catalysis has recently proved to be quite interesting.[1−4] On the other hand, use of these methods for desymmetrizing meso diols has been much less examined. An excellent result occurred in one case with meso-1,3-bis(1′-hydroxyethyl)benzene using planar chiral catalysts.[2b] With a chiral diamine as an acyl transfer catalyst, meso-1,2-diols have been desymmetrized with good yields and selectivities; however, 2-substituted-1,3-propanediols constitute a greater challenge because of the remoteness of the prostereogenic center to the hydroxyl groups and led to high ee's only if the monoacylated product was subjected to further kinetic resolution to form the meso diester thereby limiting the efficiency.[3] While enzymatic methods are highly successful in desymmetrizing meso diols,[5,6] mixed results are reported for the case of 2-substituted-1,3-propanediols.[6,7]

The nonenzymatic reactions have the advantage that either enantiomer of the catalyst normally would be equally accessible, thereby allowing access to both enantiomers of the product in the same process by simply switching the chirality of the catalyst. Our development of a novel dinuclear zinc complex formed from phenol **1** and diethylzinc (**3**) for asymmetric aldol reactions[8] raised the question of how "enzyme-like" this catalyst might behave. Zinc as a cofactor in enzymatic reactions is well known. Its ability to function as both a base and an acid suggested that it might catalyze asymmetric acylations by a different type of mechanism than the previously reported chiral transacylation catalysts.

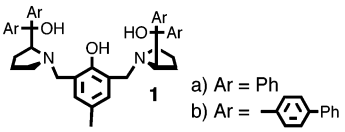
Initial work examined the desymmetrization of *cis*-cyclohexane-1,2-diol with various acylating agents including isopropenyl acetate, vinyl acetate, acetic anhydride, acetyl chloride, vinyl benzoate, and benzoic anhydride. Modest yields of the monoesters were obtained. Only in the case of acetyl chloride was an appreciable amount of diacetate formed. However, in all cases, the product was racemic. Indeed, the enantiomerically enriched monoester of this diol is rapidly racemized under the reaction conditions.

Switching to a conformationally flexible 1,3-diol should help minimize product racemization by intramolecular acyl transfer. We, therefore, turned to the difficult case of 2-substituted-propane-1,3-diols. Using vinyl acetate as the acyl transfer agent led to significant diacetylation (58%). On the other hand, vinyl benzoate reacted smoothly as shown in eq 1 using the complex derived from **1a** (Ar = Ph) to give the monobenzoate[3a,7c] as summarized in Table 1.



Dibenzoate typically formed in ≤1% yield. Thus, the ee's are not the result of a kinetic resolution of the initial monobenzoate.

Table 1. Enantioselective Acylation of 1,3-Propanediol **4**[a]

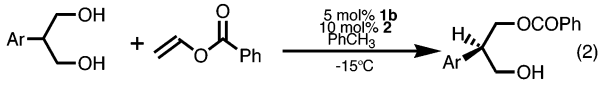


entry	ligand[b]	temp	time	yield **5**[c]	ee **5**
1	**1a**	rt	20 h	85%	74%
2	**1b**	rt	20 h	98%	83%
3	**1b**	rt	5 h	88%	84%
4	**1b**	−10 °C	20 h	99%	87%
5	**1b**	−15 °C	24 h	94%	91%
6	**1b**	−20 °C	24 h	77%	95%
7	**1b**	−40 °C	120 h	trace	n.d.

[a] All reactions were performed using 5 mol % **1**, 10 mol % **2**, and 5 equiv of **3** in toluene at 0.1 M except as indicated elsewhere. [b] Ligand **1a**, Ar = Ph; ligand **1b**, Ar = −C_6H_4−Ph−p. [c] Isolated yield of monobenzoate. Dibenzoate was formed in <1% yield (entries 1 and 4), 1% yield (entry 2), 5% yield (entry 3), or not detected (entries 5−7). [d] Reaction run with 10 mol % **1**, 20 mol % **2**, and 10 equiv of **3**.

Increasing the size of the chiral pocket by switching from **1a**, Ar = phenyl, to **1b**, Ar = 4-biphenylyl,[9] increased both yield and ee (entry 1 vs 2). On the other hand, doubling the amount of catalyst and vinyl benzoate was somewhat deleterious to yield because small amounts of dibenzoate were now isolated (entry 2 vs 3). Lowering the temperature increased the ee to a maximum of 95% (entries 4−6). Attempts to lower the temperature further led to too slow of a reaction. These results compare favorably with the best ee of 92% reported for an enzymatic desymmetrization.[7b] The absolute configuration was assigned by comparison to a known sample.[10]

With these results in hand, we examined a range of 2-arylpropane-1,3-diols as summarized in eq 2 and Table 2.[11]



Substrates bearing election-rich benzenoid rings in entries 1−3 react readily under the standard conditions to give excellent yields and ee's. Typically, dibenzoates were not detected. On the other hand, introduction of an electron-withdrawing group as in entries 4 and 5 led to slower reactions as reflected in the lower isolated yields which reflects lower conversions using 5 mol % catalyst. The lower ee's in this case may arise from some racemization of the product. Increasing the catalyst loading to 10 mol % restores the yield and ee. The naphthalene examples (entries 6 and 7) illustrate the impact of molecular shape on chiral recognition. The 2-naphthyl substrate gives excellent yield and ee. On the other hand, the placement of the benzo ring close to the two hydroxymethyl groups in the case of the 1-naphthyl substrate obviously disrupts the chiral recognition, although the reactivity is quite good. The sterically smaller thiophene leads to lower chiral recognition as compared to the benzenoid aromatics.

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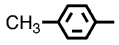
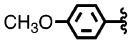
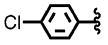
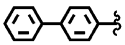
Table 2. Enantioselective Acylation of 2-Arylpropane-1,3-diols[a]

Entry	Ar	Mol% cat	Time	Yield[b]	ee[c]
1		5	24h	94%	91%[d]
2		5	24h	98%	91%
3		5	24h	99%	93%
4		10 5	18h 24h	89% 70%	90% 83%
5		10 5	18h 24h	83% 48%	86% 83%
6		10 5	18h 30h	99% 68%	59% 38%
7		10 5	18h 24h	97% 60%	93% 86%
8		10 5	20h 24h	88% 45%	74% 63%
9		10	20h	78%	70%

[a] All reactions run at 0.1 M in toluene at −15 °C. [b] Isolated yields. [c] All ee's were determined by chiral HPLC typically on a Chiralcel OJ column using heptane−2-propanol mixtures. [d] Reference 11.

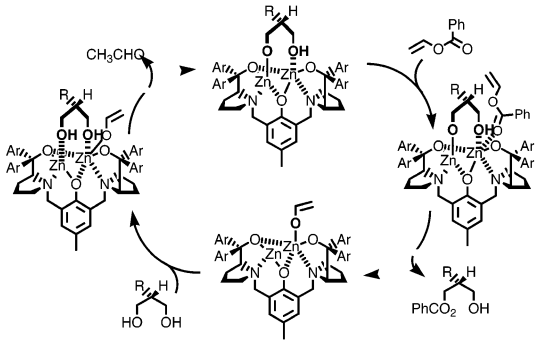
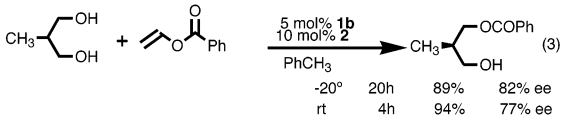


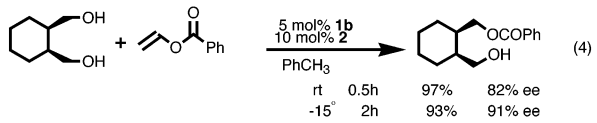
Figure 1. Catalytic cycle for desymmetrization of 2-substituted-1,3-propanediols.

2-Methylpropane-1,3-diol was also examined because the best enzymatic results gave a 70% yield of the desymmetrized product having 60% ee.[7b,12] As summarized in eq 3, this nonenzymatic catalyst gave significantly better results reaching 82% ee at −20 °C. A brief examination of a meso-1,4-diol involving primary



(3)

hydroxyl groups, which were thus more remote from the prostereogenic center, also revealed promising results. As shown in eq 4, under the standard conditions, the reaction proceeded quite fast − being complete within 0.5 h at room temperature to deliver the known benzoate[13,14] of 82% ee. Lowering the temperature to −15



(4)

°C caused virtually a complete reaction within 2 h, but the ee increased to 91%. Dibenzoate was not detected in either case. In contrast, the best enzymatic esterification with vinyl acetate using SAM II gave 44% yield of monoacetate with only 7% ee.[15] This compound proved useful in the syntheses of antiviral agents.[13]

Figure 1 depicts a proposed catalytic cycle. Coordination of the vinyl benzoate away from the diarylcarbinol unit of the prolinol followed by aryl shift to the alkoxide oxygen then accounts for the enantioselectivity. Thus, the two diarylcarbinol moieties define the chiral space responsible for the molecular recognition. It is noteworthy that this simple catalyst performs comparable to if not better than the corresponding enzymatic catalyst for similar substrates. The reactions typically require quite reasonable reaction conditions of 18−24 h at −15 to −20 °C. This catalyst represents a very promising design for desymmetrizing meso diols.

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Supporting Information Available: Experimental procedures and characterization data for monobenzoates of Table 2, eq 3, and eq 4 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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