Kinetic Resolution of Secondary Alcohols. Enantioselective Acylation Mediated by a Chiral (Dimethylamino)pyridine Derivative

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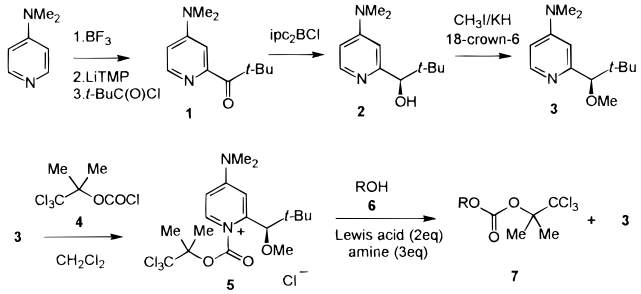
Kinetic resolution of certain chiral alcohols or their ester derivatives can be carried out using the lipase/esterase family of acyl transfer catalysts.[1] If the enantiomers differ in relative reactivity by a factor (*s*) of 100 or more, >40% recovery of each enantiomer is theoretically possible with >90% ee.[1a] However, lower enantioselectivities *s* in the range of 10−30 are often encountered, and purified yields can be considerably lower. In such cases the less reactive enantiomer can still be obtained with high ee by forcing the conversion well past the theoretical 50% optimum because eventual destruction of the more reactive enantiomer compensates for "errors" in enantioselective recognition. However, higher ee is achieved at the cost of decreased material recovery.[1a]

Some progress has been made with enantioselective nonenzymatic acylating agents.[2−4] The best selectivities to date were reported by Evans *et al.* using a 10-fold excess of racemic alkoxides $ArCH(CH_3)OMgBr$ and a chiral *N*-acyl imide as the stoichiometric acyl donor.[3] At ca. 10% conversion of the alkoxide, this system gave up to 90% enantiomer excess in the product esters, corresponding to *s* (calculated ratio of rate constants for the more reactive vs the less reactive enantiomer)[5] in the range of 20−30. The best *s* values reported using a chiral *nonenzymatic* catalyst and an *achiral* acyl donor as the stoichiometric reagent are considerably lower.[2a,b,e,h,4] Under conditions where catalyst turnover is demonstrated, only one example is known where *s* is greater than 10.[4]

We now describe chiral acyl transfer agents based on the *p*-(dimethylamino)pyridine (DMAP) nucleus.[6] The new reagents must be employed in stoichiometric amounts, but the chiral DMAP derivatives are recovered unchanged at the end of the reaction and can be reused. By analogy to Kessar's results with pyridine,[7] DMAP was activated by conversion into the BF_3 adduct. Metalation at C_2 with lithium tetramethylpiperidide (LiTMP) followed by reaction with pivaloyl chloride then gave the ketone **1** (61%) together with recovered DMAP (10%) and the 2,6-dipivaloyl derivative (15%). Reduction of **1** using (−)-



B-chlorodiisopinocampheylborane (ipc_2BCl)[8] produced **2** (71%; 96% ee), and recrystallization afforded material with >99% ee according to HPLC assay. Methylation (CH_3I/KH/18-crown-6) then produced the key reagent **3** (absolute configuration assigned by analogy to the pyridine reduction precedent of Bolm *et al.*).[8]

Treatment of **3** with the commercially available chloroformate **4** generated the corresponding pyridinium salt **5** as evidenced by characteristic ^1H NMR downfield shifts for the ring protons (δ 8.06, 6.56, 6.49 ppm for **3**; 8.29, 6.69, 6.67 ppm for **5** in CD_3CN). The solution containing **5** did not acylate representative secondary alcohols at room temperature. However, the addition of a tertiary amine together with a Lewis acid (anhydrous $ZnCl_2$ or $MgBr_2$) initiated a slow acyl transfer reaction (15−40 h for consumption of **5** using 2 equiv of the racemic secondary alcohol **6**, ca. 20 °C), resulting in the formation of the mixed carbonate **7**. Product assay was performed by ^1H NMR on the mixture of **6** and **7** to measure percent conversion, and the ee of esters **7** was established by HPLC assay on a chiral support after purification of **7** and saponification to the original alcohol **6** (see supporting information). In all entries, the material balance (**6** + **7**) was at least 90%, calculated from the isolated yield of purified **7** and from the ratio of **6**:**7** determined by NMR. According to this evidence (Table 1), several of the mixed carbonate esters **7** were formed with >90% enantiomeric purity at conversions in the 20−42% range.[9] Several entries in Table 1 report *s* values well above 30 (calculated from product ee and percent conversion),[5] the best results observed to date with any nonenzymatic acylating agent.

As expected, the ee of unreacted **6a** was improved by doubling the amount of reagents to increase the percent conversion (96% ee at 71% conversion; 60% ee at 42% conversion). However, the improvement was less than calculated (>99% ee) based on $s = 42$.[5] The reason for the discrepancy was not identified, but possible explanations include minor racemization of **6a**, integral error in the percent conversion, or interference by the product **7a** in the enantioselective acylation.[10] The increased conversion experiments were not pursued further because they require a larger proportion of the valuable reagent **5**. Thus, it is more practical to control conversion so that *product* (not unreacted substrate **6**) ee and

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(9) Procedure for kinetic resolution of 1-arylethanol derivatives: to the solution of **3** (0.15 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added a CH_2Cl_2 solution of **4** (0.14 mmol, Aldrich). The mixture was warmed to room temperature and stirred for 2 h. A solution of anhydrous (fused) $ZnCl_2$ (0.3 mmol, 0.5 M) in diethyl ether was then added. After 10 min, the racemic **6** (0.3 mmol) and triethylamine or PMP (0.45 mmol) were added sequentially. The solution was stirred at room temperature under N_2 for the specified time (Table 1), and the neutral products were separated by flash chromatography prior to assay.

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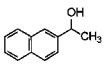
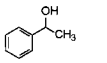
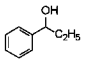
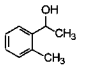
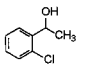
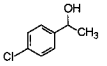
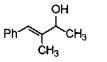
Table 1. Enantioselective Acylation of Secondary Alcohols with **5**

ROH	Entry	Lewis Acid	Amine	Time (h)	Conversion (%)	Recovered ROH ee (%)	Product ee (%)[a]	Enantioselectivity s[b]
 **6a**	1	$ZnCl_2$	TEA[d]	52	28	33 (R)[c]	94 (S)[c]	44
	2	$ZnCl_2$	TEA[d]	39	30	38	91	31
	3	$MgBr_2$	TEA[d]	17	54	87	84	48
	4	$MgBr_2$	TEA[d]	14	42	60	91	42
 **6b**	5	$ZnCl_2$	TEA[d]	52	24	30 (R)[c]	94 (S)[c]	45
	6	$ZnCl_2$	TEA[d]	40	32	NA	90	29
	7	$ZnCl_2$	PMP[d]	20	47	73	87	36
	8	$MgBr_2$	TEA[d]	20	54	83	82	39
 **6c**	9	$ZnCl_2$	TEA[d]	40	25	NA (R)[c]	93 (S)[c]	38
	10	$ZnCl_2$	PMP[d]	40	42	51	82	19
	11	$MgBr_2$	TEA[d]	40	41	NA	82	18
 **6d**	12	$ZnCl_2$	TEA[d]	62	20	22 (R)[c]	89 (S)[c]	22
	13	$ZnCl_2$	PMP[d]	40	41	49	83	19
	14	$MgBr_2$	TEA[d]	40	39	NA	76	12
 **6e**	15	$ZnCl_2$	TEA[d]	68	22	20 (R)[e]	93 (S)[e]	37
	16	$ZnCl_2$	TEA[d]	48	21	19	92	29
	17	$ZnCl_2$	PMP[d]	43	39	59	93	53
	18	$MgBr_2$	TEA[d]	41	48	74	85	30
 **6f**	19	$ZnCl_2$	TEA[d]	48	31	41 (R)[e]	90 (S)[e]	27
	20	$ZnCl_2$	TEA[d]	51	19	21	92	29
	21	$ZnCl_2$	PMP[d]	38	43	66	90	40
	22	$MgBr_2$	TEA[d]	40	44	69	89	36
 **6g**	23	$ZnCl_2$	TEA[d]	48	20	21 (R)[e]	90 (S)[e]	24
 **6h**	24	$ZnCl_2$	TEA[d]	60	10	7 (R)[f]	83 (S)[f]	11
	25	$MgBr_2$	TEA[d]	60	40	37	78	14

[a] HPLC assay. [b] Enantioselectivity calculated from percent conversion and product ee;[5] error in *s*: see footnote 10. [c] Configuration established by comparison with commercial material. [d] TEA = triethylamine; PMP = 1,2,6-pentamethylpiperidine. [e] Reference 11. [f] Reference 12.

recovery are maximized, in contrast to typical lipase experiments.

Neither the tertiary amine nor the Lewis acid were sufficient to induce substantial conversion of **5** to the mixed carbonate **7** at room temperature unless both were present. Addition of the Lewis acid *prior to* the addition of **4** resulted in nearly racemic product, perhaps due to catalysis of the reaction between **4** and **6** by the tertiary amine. Relatively fast acylations were observed using **5** activated by the $ZnCl_2$/PMP combination compared to the $ZnCl_2/Et_3N$ combination. This is probably because the hindered amine PMP (1,2,2,6,6-pentamethylpiperidine) can still function as a basic catalyst without binding the Lewis acid as strongly as does Et_3N. A smaller accelerating effect was observed for PMP with $MgBr_2$ as the Lewis acid. Since the $MgBr_2$ experiments were inherently faster than with $ZnCl_2$ as the Lewis acid, the PMP/$MgBr_2$ conditions were not explored in detail. All of the reactions were sensitive to moisture and to the purity of reactants, and failure to control these variables resulted in decreased enantioselectivity.

Isobutyl chloroformate gave minimal product ee with the usual combination of **3**/$ZnCl_2/Et_3N$ and **6a** as the substrate, and an attempt to use *tert*-butyl chloroformate in a similar experiment failed because of decomposition of the chloroformate. Simple acyl chlorides (pivaloyl; benzoyl) were ineffective in place of **4** (nearly racemic ester products). Zinc triflate was comparable to $ZnCl_2$ or $MgBr_2$, but the other Lewis acids tested gave slow acylation ($CeCl_3$; $SnCl_4$; $Yb(OTf)_3$) or caused the formation of side products ($TiCl_4$; $ZrCl_4$; $AlCl_3$). Boron trifluoride etherate did promote acyl transfer from **5**, but selectivity was low ($s < 2$), and the sense of enantioselection with **6a** was opposite to that seen with $ZnCl_2$ or $MgBr_2$ under the usual conditions. These results leave open the possibility that the activated form of **5** is a zinc or magnesium complex with the metal ion chelated by the carbonyl and ether oxygens, but much remains to be learned about this complicated system, and we will not speculate further regarding the nature of the acyl transfer step or other mechanistic issues.

Because **3** is the starting material for the above process and because it is recovered unchanged after aqueous workup (no change in ee after five repeated acylation cycles), the chiral DMAP derivative satisfies one of the definitions of a catalyst. Of course, **3** is used in stoichiometric quantity and does not turn over under the acylation conditions. Preliminary attempts to achieve turnover by altering stoichiometry and the order of mixing the reagents were not successful, but many options remain to be explored.

In summary, we have described a nonenzymatic system for kinetic resolution of secondary benzylic alcohols by enantioselective acylation that approaches some of the lipase methods in enantioselectivity. Enantiomerically enriched products can be obtained in several cases in 20−44% yield (based on the racemic starting material; 50% theoretical yield limit) with ca. 90% ee. These results are not competitive with the best lipase experiments, but they suggest that nonenzymatic acyl transfer alternatives may be capable of acceptable levels of selectivity. Experiments intended to improve practicality and to achieve catalyst turnover are in progress.

Acknowledgment. This work was supported by the National Science Foundation.

Supporting Information Available: Experimental details for preparation of **1**−**3**, characterization data for **1**−**3** and **7**, detailed procedures for acylation; and HPLC assay methods for enantiomers of **6** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(10) Discrepancies were also encountered with some of the entries in Table 1 when *s* values calculated from the ee of recovered **6** were compared with *s* based on ee of the product (**7**).[5] Due to the logarithmic nature of the calculation, as little as 5% undetected impurity, side reaction, racemization, or integral error (used to measure percent conversion) could account for the discrepancy in *s* values. At most, traces (<1%) of racemization were detected by exposing **6e** to zinc chloride + (PMP), or with added **3**, or with PMP·HCl added (HPLC assay). Racemization cannot be ruled out, but error in percent conversion is the more likely source of the discrepancy. However, racemization of product ester or the recovered alcohol may explain why marginal results were obtained with the sensitive 1-(2-methoxyphenyl)-ethanol (maximum 15−30% ee for the ester as well as the recovered alcohol).

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