Enantioselective Acylations Catalyzed by Chiral Phosphines

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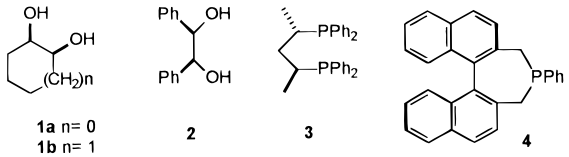
More than 60 years ago, Wegler demonstrated significant enantiomer enrichment by reacting secondary alcohols with acetic anhydride in the presence of alkaloid catalysts at 100 °C.[1] Many similar kinetic resolutions can now be performed with the lipase/esterase catalysts,[2] but nonenzymatic methods are still in the developmental stage.[3,4]

We report the first examples of enantioselective acylation using chiral phosphine catalysts. As expected from prior work,[5,6] diarylalkylphosphines were not sufficiently reactive. Thus, 1,2-diphenylphosphinoethane gave <5% acyl transfer from acetic anhydride to representative secondary alcohols (24 h). Faster acylation occurred with the 1,3-diphosphine **3**,[7] but with low selectivity (9% ee in CD_2Cl_2) in the monoacetylation of *cis*-cyclohexane-1,2-diol (**1b**) (see Table 1). The corresponding reaction of **2**



was encouraging (monoacetate, 48% ee). On the other hand, poor results were obtained with **4**[8] as the catalyst: **1b**, monoacetate, 11% ee; **2**, monobenzoate, 22% ee. The bis-phosphine **5** gave no acylation, but the less hindered **6a** and **6b** (Burk et al.)[9] were more reactive catalysts and gave the first indications of potentially useful selectivity.

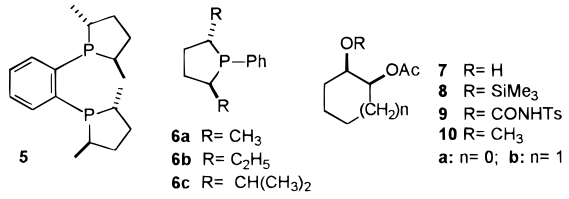


Table 1. Enantioselective Acylations Catalyzed by Chiral Phosphines (CH_2Cl_2 or CD_2Cl_2, rt)

substrate	catalyst	anhydride	product ee (% convsn)	selectivity[a] (*s*)
1b	3	$(CH_3CO)_2O$	9 (40)	1.2
1b	4	$(CH_3CO)_2O$	11 (60)	1.3
1b	6a	$(CH_3CO)_2O$	62−7 (66)	4.3−5.1
1b	6b	$(CH_3CO)_2O$	40−45 (80)	2.6
1a	6a	$(CH_3CO)_2O$	52 (10)[b]	3.2[b]
2	3	$(CH_3CO)_2O$	48−53 (30−73)	2.9
2	6a	$(CH_3CO)_2O$	27 (22)	1.2
2	4	$(C_6H_5CO)_2O$	22 (31)	1.6
2	6a	$(C_6H_5CO)_2O$	68 (84)	5.5
2	6b	$(C_6H_5CO)_2O$	58 (70)	4.7
$PhCH(OH)CH_3$	6a	$(CH_3CO)_2O$	34 (44)	2.7
$PhCH(OH)CH_3$	6a	$(m\text{-}ClC_6H_5CO)_2O$	34 (51)	2.8
PhCH(OH)-*t*-Bu	6a	$(CH_3CO)_2O$	19[c] (27)	3.8
PhCH(OH)-*t*-Bu	6a	$(m\text{-}ClC_6H_5CO)_2O$	81 (25)	12−15

[a] Estimated rate ratio of faster reacting to slower reacting hydroxyl configuration calculated according to ref 15. [b] Selectivity based on ee at 10% conversion; product racemizes upon longer exposure to the reagents. [c] Unreacted starting material ee is given in this case; product ee was not assayed.

The desymmetrization of **1b** using 5-8 mol % **6a** + acetic anhydride in dichloromethane in the temperature range of 0−20 °C produced the monoacetate **7b** with 62−67% ee (GLPC or HPLC assay). Somewhat lower selectivity (45% ee) was observed with **6b**, while the more hindered **6c** afforded nearly racemic material in a much slower reaction. Considerable care was necessary to assay ee because **7b** was readily racemized by acetyl migration, especially upon prolonged exposure to silica gel.[10] However, self-consistent assay results were obtained using several techniques: method 1, silylation, followed by GLPC analysis of **8** on a chiral support; method 2, treatment with Ts-N=C=O (spontaneous, exothermic derivatization!) followed by HPLC assay of **9** on a chiral stationary phase; method 3, conversion to **10** and **11** (see below), followed by HPLC assay of the derived 3,5-dinitrobenzoate ester (chiral support). To establish absolute configuration of the major enantiomer, **7b** was transformed into the methyl ether **10b** by reaction with Me_3SiCHN_2,[11] the ester group was saponified to afford **11b**, and the resulting hydroxyl function was esterified with (1*S*)-camphanic chloride. This sequence produced a mixture of diastereomeric esters which afforded crystals of the major isomer **12** (for convenience, the minor diastereomer is not illustrated throughout the sequence from diastereomerically enriched **7b** to **12**), and the structure was established unequivocally by X-ray crystallography.

The enantiomeric purity of **7b** did not change as a function of percent conversion, a result that rules out racemization via intramolecular acetyl transfer over the course of the experiment. On the other hand, the five-membered analog **7a**[12] did racemize upon exposure to

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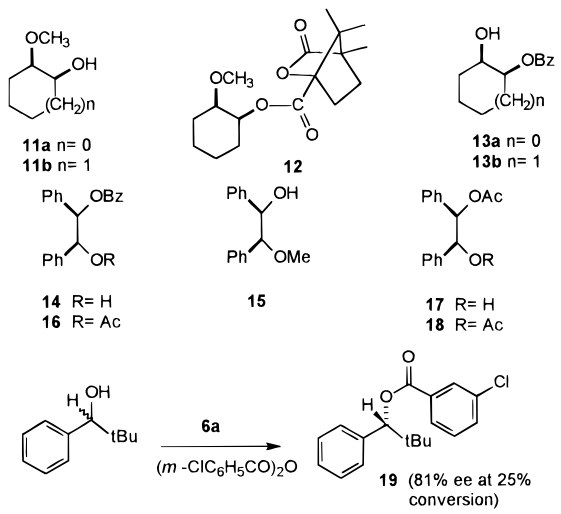

phosphine **6a** in control experiments, and attempted enantioselective acetylation proved to be strongly time dependent. Thus, according to assay method 2, above, monoacetate **7a** was formed with 52% ee at 10% conversion (65 min), but only 28% ee at 67% conversion (200 min). The absolute configuration of **7a** was not established with the same degree of rigor as for **7b**, but the tentative assignment is supported by the similarity of HPLC retention data for the 3,5-dinitrobenzoate esters of **11a** and **11b** relative to their enantiomers on the same chiral support. Analogous results were obtained in catalyzed benzoylations. The six-membered **1b** afforded **13b** (55% ee) without significant change in ee over time,[13a] but five-membered **1a** produced **13a** with 15% ee after 14 h (44% conversion) and <2% ee after 51 h (71% conversion).[13b] The benzoylations were significantly slower compared to the acetylations in all cases, as shown by the longer reaction times required to reach similar levels of conversion. The configurations of **13a** and **7a** were correlated via **11a** using method 3.

Attempts to catalyze the benzoylation of **2** with diphosphine **3** failed because the reaction was too slow. However, the combination of either **6a** or **6b** and benzoic anhydride was effective and afforded the monobenzoate **14** with a promising level of enantiomeric excess (69% or 58% ee, respectively).[14a] This material could be enriched further by simple crystallization methods. Thus, **14** (58% ee) was allowed to crystallize from ethyl acetate–hexane, and the first crop of racemic material was removed. Recrystallization of the mother liquor gave **14** with 93% ee (second crop; 14% recovery based on **2**) and 84% ee (third crop; 16%). To establish absolute configuration, the enriched sample of **14** was converted into the known methyl ether **15** by the same sequence of methylation (Me_3SiCHN_2/HBF_4) and saponification as also used in the assay of **7**, and absolute configuration was assigned from a comparison of the reported sign of optical rotation for **15**.[14b]

A second technique for upgrading the enantiomeric purity of monobenzoate **14** was found, based on kinetic resolution. Thus, treatment of **14** with acetic anhydride and **6a** as the catalyst was monitored over time. The minor enantiomer (not drawn) proved to be more reactive, and the enantiomer excess of unreacted **14** was found to improve as a function of percent conversion to the diester **16**. Thus, allowing the acetylation of **14** (69% ee) to reach 33% conversion to **16** afforded 59% recovered benzoate **14** with 89% ee. As in other kinetic resolutions,[15] the % ee of recovered **14** could be increased by driving the acetylation reaction further toward complete conversion, but improved ee resulted in lower recovery of enriched **14**. The technique succeeds because *ent*-**14** has the more reactive configuration at the residual OH group.

Acetylation of *meso*-hydrobenzoin **2** using acetic anhydride gave modest selectivity for **17** using either the diphosphine **3** (48% ee) or the phospholane **6a** (27% ee) as catalysts. When enriched monoacetate **17** (27% ee) was treated with **6a** + acetic anhydride, recovered **17** showed improved ee with increasing conversion to the diacetate **18**. The reaction had to be forced to higher conversion (85%; 32 h at rt) than in the case of **14** to reach acceptable levels of enantiomeric purity (89% ee; ca. 10% recovery of **17**) due to lower enantioselectivity in the conversion from **17** to **18**. The cyclohexanediol-derived monoacetate **7b** was also tested for kinetic resolution in a second acetylation step using **6a** + acetic anhydride, but no improvement in ee was observed (negligible enantioselectivity).

The combination of **6a** and acetic anhydride gave poor enantioselecetivity with racemic secondary alcohols of the general formula PhCH(OH)R. Selectivities s[15] increased modestly from s = ca. 2 to s = ca. 4 as the bulk of R was increased from CH_3 to $C(CH_3)_3$. Benzoylations were unacceptably slow, but the reactivity could be increased using *m*-chlorobenzoic anhydride.[16] With 16 mol % of **6a** as the catalyst, $PhCH(OH)CH_3$ reacted at room temperature, but with marginal selectivity (s = ca. 3; 34% ee). On the other hand, $PhCH(OH)C(CH_3)_3$[17] was converted into the *R* ester **19** with 81% ee at 25% conversion while the unreacted alcohol was recovered with 29% ee. These values correspond to s = 12 (based on product ee) or s = 15 (based on unreacted alcohol ee). The result is mediocre by comparison to representative lipase resolutions,[2] and it also falls short of the selectivity levels achieved for several other substrates by Evans et al. (stoichiometric acylation conditions).[3] Nevertheless, the enantioselectivity (s = 12-15) surpasses that reported for any nonenzymatic system where the acyl donor is achiral and where catalytic turnover of the chiral agent is demonstrated.[18]

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Supporting Information Available: Experimental details for desymmetrization, kinetic resolution, and assay methods; characterization data for **12** (7 pages).

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