Parallel Kinetic Resolution under Catalytic Conditions: A Three-Phase System Allows Selective Reagent Activation Using Two Catalysts

Edwin Vedejs* and Eriks Rozners

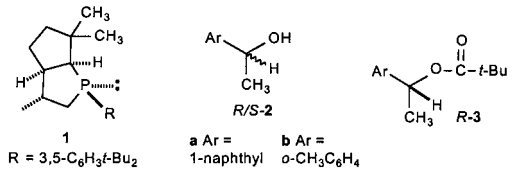
Department of Chemistry, University of Michigan
Ann Arbor Michigan 48109

Received September 29, 2000

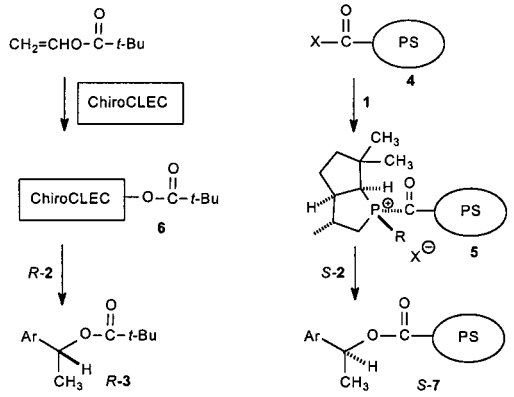
We have been interested in experiments where two different catalysts are present, each of which must activate a unique substrate. This situation would arise in some of the conceivable catalytic adaptations of parallel kinetic resolution (PKR).[1−3] As reported in the initial publication describing a stoichiometric version of the PKR experiment, two quasi-enantiomeric reagents can be used to simultaneously derivatize each enantiomer of a racemic mixture to give two distinct quasi-enantiomeric products. In the optimal case where the competing derivatizations occur with similar rates and complementary enantioselectivities, product ee is near the theoretical limit calculated from the inherent enantioselectivities[4] regardless of % conversion, and recovery can exceed 90%.

PKR experiments that rely on two parallel *catalytic* reactions would be especially attractive. Related examples are known for the special case where a single chiral catalyst induces the formation of a distinct product from each substrate enantiomer.[5] However, a unique scenario should be possible where two different catalysts are used to promote the selective derivatization of each enantiomer. Such an experiment allows interesting options for the separation of the quasi-enantiomeric products as discussed later, but it requires that each catalyst must selectively activate only one of the two derivatizing reagents. To achieve the required selectivity in a fully catalytic version of PKR, we have used a technique based on phase isolation as described below.

The experimental design features the simultaneous use of a commercial cross-linked lipase acylation catalyst (ChiroCLEC-PC)[6a] together with a lipase-specific acyl donor, a complementary chiral phosphine acylation catalyst **1**,[7] and a phosphine-specific acyl donor to derivatize enantiomeric alcohols **2**. Control experiments with aryl carbinol substrates identified vinyl pivalate as an acyl donor that is activated by ChiroCLEC-PC,[6] but not by the phosphine **1**, and confirmed that ChiroCLEC-PC has the standard lipase reactivity preference for the formation of the *R*-ester (for example, **3a** with **s** = 83).



Furthermore, lipase selectivity or reactivity were not significantly affected when the phosphine **1** was present together with the vinyl pivalate. On the other hand, the usual phosphine catalyzed isobutyric anhydride acylation[7] of the alcohol could not be performed in the presence of ChiroCLEC-PC because the latter also activates the anhydride. To avoid this problem, and to ensure selective activation of a unique acyl donor by the lipase, we considered a polymer-bound reagent to serve as the phosphine-specific acyl donor. Insoluble activated esters of the general formula **4** cannot interact with ChiroCLEC-PC because the latter does not dissolve in organic solvents. The catalytic PKR experiment would then consist of three phases,[8] (1) ChiroCLEC-PC (insoluble catalyst), (2) insoluble acyl donor **4**, and (3) soluble catalyst **1** and soluble acyl donor (vinyl pivalate). The three-phase system should allow contact between **1** and **4** to generate **5**, as well as the usual interaction between ChiroCLEC-PC and the vinyl ester to produce the acylated lipase intermediate **6**. Since the reactive acylphosphonium salt **5** is insoluble, there is no possibility that it would modify or deactivate the lipase. Furthermore, the eventual ester product **7** is attached to the solid phase and would be easy to separate from the quasi-enantiomeric lipase-derived ester *R*-**3** because the latter is formed in solution.



Several structural options were evaluated for the phosphine-selective acyl donor. According to preliminary experiments under homogeneous conditions, the nature of the leaving group X is important for enantioselectivity as well as reactivity. Best results were obtained when X is carboxylate, but the corresponding polymer bound reagent **4** would then contain mixed anhydride functionality with the potential for reaction at either carbonyl

(1) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584.

(2) (a) Review: Eames, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 885. (b) Early analogy: Horeau, A. *Tetrahedron Lett.* **1961**, *2*, 506. (c) Pietrusiewicz, K. M.; Holody, W.; Koprowski, M.; Cicchi, S.; Goti, A.; Brandi, A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *144*−*146*, 389. Cardona, F.; Valenza, S.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **1999**, 1319. Guo, J.; Wu, J.; Siuzdak, G.; Finn, M. G. *Angew. Chem., Int. Ed*. **1999**, *38*, 1755. Pedersen, T. M.; Jensen, J. F.; Humble, R. E.; Rein, T.; Tanner, D.; Bodmann, K.; Reiser, O. *Org. Lett.* **2000**, *2*, 535.

(3) For a precedent involving two or more enzymatic catalysts and conversion of one of the enantiomers into an achiral product, see: Brooks, D. W.; Wilson, M.; Webb, M. *J. Org. Chem.* **1987**, *52*, 2244.

(4) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(5) (a) El-Baba, S.; Poulin, J.-C.; Kagan, H. B. *Tetrahedron* **1984**, *40*, 4275. Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493. Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021. Visser, M. S.; Hoveyda, A. H. *Tetrahedron* **1995**, *51*, 4383. Bolm, C.; Schlinghoff, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1247. (b) Overview: Kagan, H. *Croat. Chem. Acta* **1996**, *69*, 669. (c) Parallel reactions involving steady-state partitioning of diastereomeric intermediates: DeMello N. C.; Curran D. P. *J. Am. Chem. Soc.* **1998**, *120*, 329.

(6) (a) Khalaf, N.; Govardhan, C. P.; Lalonde, J. J.; Persichetti, R. A.; Wang, R.-F.; Margolin, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 5494. (b) Use of vinyl esters with lipases: Degueil-Castaing, M.; De Jeso, B.; Drouillard, S.; Maillard, B. *Tetrahedron Lett.* **1987**, *28*, 953; Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 3128.

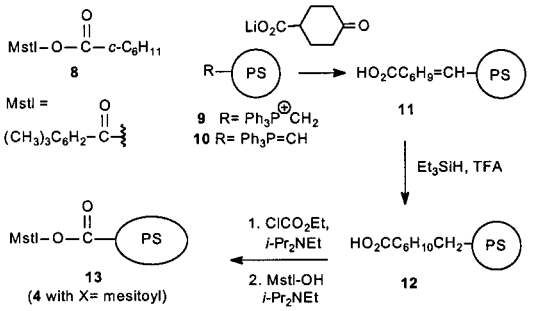
(7) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813.

(8) (a) Rebek, J.; Brown, D.; Zimmerman, S. *J. Am. Chem. Soc.* **1975**, *97*, 454. Pittman, C. U., Jr.; Smith, L. R. *J. Am. Chem. Soc.* **1975**, *97*, 1749. Regen, S. L. *Angew. Chem.* **1979**, *91*, 464. (b) Related multiphase chemistry: Cohen, B. J.; Kraus, M. A.; Patchornik, A. *J. Am. Chem. Soc.* **1981**, *103*, 7620. Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1985**, *26*, 1305. Bergbreiter, D. E.; Zhang, L. *J. Chem. Soc., Chem. Commun.* **1993**, 596. Parlow, J. J. *Tetrahedron Lett.* **1995**, *36*, 1395. Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882. Gerritz, S. W.; Trump, R. P.; Zuercher, W. J. *J. Am. Chem. Soc.* **2000**, *122*, 6357.

10.1021/ja0035405 CCC: $20.00
Published on Web 02/15/2001

group. Sterically differentiated mixed anhydride **13** (**4** with X = mesitoate) should allow selective carbonyl activation, but the mesitoate anion would also play a role in proton transfer and enantioselectivity in the phosphine-catalyzed acylation. This issue was probed under homogeneous conditions. The model mixed anhydride **8** was generated by the reaction of cyclohexanecarboxylic acid chloride with mesitoic acid and triethylamine. Anhydride **8** could not be purified, but promising enantioselectivity was determined when crude **8** was used in a simple kinetic resolution of **2a** with phosphine **1** as the catalyst at room temperature (**s** > 25).[9] Mesitoate ester formation was not detected, and the *S*-enantiomer of **2a** was more reactive, as required for a complementary match with the enantioselectivity of the lipase catalyst in PKR.

A polymer-bound cyclohexanecarboxylic acid **12** was then prepared from phosphonium salt **9** using standard methods.[10] Thus, **9** was converted to the ylide **10** with *n*-butyllithium and 4-oxocyclohexanecarboxylic acid was added as the lithium salt in THF−DMPU. The resulting **11** was reduced using Et_3SiH/CF_3CO_2H to afford **12** and conversion into the mixed anhydride **13** was performed by reaction with ethylchloroformate, *N*,*N*-diisopropylethylamine, and mesitoic acid.



The polymer-bound anhydride **13** was tested in a simple kinetic resolution at room temperature with **2a** as the substrate and **1** as the catalyst. A satisfactory value of **s** = 34 was determined after cleavage of the ester **7a** using Bu_4NOH/THF, and a preference for acylation of *S*-**2a** was confirmed. Such high enantioselectivity requires that transport of both enantiomers of **2a** into and out of the polymer is fast on the time scale of the acyl transfer process. A positive result was anticipated because there are prior examples of kinetic resolution using polymeric reagents.[11]

With all of the preliminary conditions for catalytic PKR satisfied, the key experiment could be examined. Both catalysts (**1** and ChiroCLEC-PC) were used together with *R*/*S* **2a** and the catalyst-specific acyl donors, **13** and vinyl pivalate. Based on three experiments with conversions in the range of ∼85−90%, PKR was clearly demonstrated. Thus, *S*-**2a** was recovered after cleavage of polymer-bound **7a** with ee values of 93, 91, and 92%, while the (soluble) pivalate *R*-**3a** was obtained with 97, 94, and 96% ee, respectively.[12] In view of the high (≥85%) conversions, product recoveries, and enantiomeric purities, the conditions required for catalytic PKR must have been satisfied.

Good enantiomeric purity in *both* products *R*-**3a** and *S*-**7a** was obtained even though the enantioselectivities of the two catalysts were not closely matched (**2a** with ChiroCLEC-PC/vinyl pivalate: **s** = 83; **2a** with phosphine **1**/mixed anhydride **13**: **s** = 34). This is possible because the more important variable in PKR is the rate of each of the *major* pathways from *R*/*S*-**2a** to the products *R*-**3a** and *S*-**7a**. If catalyst **1** consumes *S*-**2a** at nearly the same rate that Chiroclec-PC consumes *R*-**2a**, then the ratio of unreacted *S*-**2a**:*R*-**2a** will remain close to unity, provided that the rates leading to the *minor* products *S*-**3a** and *R*-**7a** are sufficiently slow. This condition must have been satisfied because *R*-**3a** and *S*-**7a** were obtained with ee values near the theoretical limits (defined as the ee expected at <1% conversion in a simple kinetic resolution, 98% ee for *R*-**3a** with **s** = 83, and 94% ee for *S*-**7a** with **s** = 34). The limits were not reached because enantioselectivities for the two parallel reactions were not identical.

The ratio of unreacted *S*-**2a**:*R*-**2a** in the catalytic PKR experiments was assayed at varying conversions. In all three experiments, unreacted alcohol developed a small initial excess of *R*-**2a** with the maximum (6−13% ee) found at 40−70% conversion. As % conversion increased beyond .∼70%, the ee value of unreacted **2a** decreased and eventually inverted in favor of *S*-**2a**. The empirical results indicate that the phosphine-catalyzed acylation with **13** becomes relatively less efficient compared to the ChiroCLEC-PC acylation as % conversion increases.

It is instructive to compare the ee values of unreacted starting material and products in the PKR experiment vs the simple kinetic resolution of **2b**, a substrate that reacts with relatively modest enantioselectivity at room temperature using either catalyst (**2b** with ChiroCLEC-PC/vinyl pivalate: **s** = 37; **2b** with phosphine **1**/mixed anhydride **13**: **s** = 23). The PKR experiment gave *S*-**7b** with 89% ee and *R*-**3b** with 94−5% ee and >80% recovery. According to Kagan's equation,[4] the simple kinetic resolution experiment at 50% conversion using **1** as the catalyst (**s** = 23) would afford unreacted *R*-**2b** and product *S*-**3b**, each with 81% ee. At 54% conversion, the unreacted *R*-**2b** (46% recovery limit) would have the same 89% ee as in the PKR experiment, but the product *S*-**3b** would have 77% ee, too low for most purposes. Increased conversion to 56% would increase the ee of unreacted *R*-**2b** to 94%, but recovery of useful material would decrease (44% maximum) and the ee of *S*-**3b** would drop further to 74%.[13]

The above findings constitute a proof for the concept of PKR using two different chiral catalysts to selectively activate two different achiral stoichiometric reagents. The results also show that PKR succeeds even when the enantioselectivities of the competing simultaneous reactions are not closely matched and when the ratio of unreacted enantiomers deviates from the ideal 1:1 ratio in a nonlinear manner.

Phase isolation provides one way to control which reagent is activated by a given catalyst. Several variations on the phase isolation theme remain to be explored, including the case where each catalyst is placed in separate imiscible phases. In principle, however, catalytic PKR experiments need not be performed using phase isolation. Parallel reactions based on two mechanistically distinct catalytic derivatizations should be feasible using two different catalysts under homogeneous conditions. Efforts are under way to identify PKR examples where this might be possible. Similar considerations apply to any set of four potentially competing catalytic reactions induced by two catalysts, and the same principle could be used to differentiate or separate two diastereomers, regioisomers, or components of a mixture.

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

Supporting Information Available: Preparation of solid-phase reagents; general procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0035405

(9) The empirical selectivity is listed in all cases without correcting for the enantiomeric purity of catalyst **1** (99%).

(10) Frechet, J. M.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492.

(11) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147. Coisne, J. M.; Pecher, J. *Chimia* **1981**, *35*, 97. Annunziata, R.; Borgogno, G.; Montanari, F.; Quici, S.; Cucinella, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 113.

(12) A fourth experiment was interrupted at 75% conversion, resulting in *R*-**3a** (97% ee) and *S*-**7a**, 89% ee after cleavge.

(13) Leading references to recent nonenzymatic catalysts for simple kinetic resolution: (a) Review: Spivey, A. C.; Maddaford, A.; Redgrave, A. J. *Org. Prep. Proced. Int.* **2000**, *32*, 331. (b) Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun. (Cambridge)* **2000**, 1009. (c) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154. (d) Sano, T.; Miyata, H.; Oriyama, T. *Enantiomer* **2000**, *5*, 119. (e) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638.