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Catalytic Parallel Kinetic Resolution under Homogeneous Conditions

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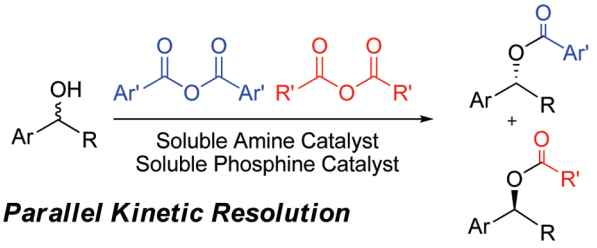

Two complementary chiral catalysts, the phosphine **8d** and the DMAP-derived *ent*-**23b**, are used simultaneously to selectively activate a mixture of two different achiral anhydrides as acyl donors under homogeneous conditions. The resulting activated intermediates **25** and **26** react with the racemic benzylic alcohol **5** to form enantioenriched esters (*R*)-**24** and (*S*)-**17** by fully catalytic parallel kinetic resolution (PKR). The aroyl ester (*R*)-**24** is obtained with near-ideal enantioselectivity for the PKR process, but (*S*)-**17** is contaminated by ca. 8% of the minor enantiomer (*R*)-**17** resulting from a second pathway via formation of mixed anhydride **27** and its activation by **8d**.

Introduction

The kinetic resolution (KR) of racemic mixtures is a powerful method for obtaining enantioenriched substances.[1] Even with relatively modest enantioselectivity, s (k_{fast}/k_{slow}) = 20 or above, a substantial fraction of the less reactive enantiomer can be recovered with >90% ee if the reaction is run to ≥55% conversion. However, this approach usually results in <50% recovery of highly enriched material due to the well-known consequence of competition kinetics and the problem of mass action. As the faster-reacting enantiomer is consumed, the ratio of less reactive to more reactive enantiomers increases, and eventually, only the less reactive enantiomer remains. This is the key advantage of KR, but it ensures that conversion of the slower reacting enantiomer competes increasingly over time. One consequence is that the *product* of simple KR cannot be obtained with acceptable yield and ee unless s is of the order of 200 or better.[1,2] Over the past decade, nonenzymatic catalysts have begun to reach this level of enantioselectivity, but applications that exploit enantioenriched *products* of KR remain quite rare.

Two strategies have been developed that avoid the mass action problem by maintaining the enantiomer ratio near 1:1 throughout the reaction, (1) dynamic kinetic resolution (DKR)[3] and (2) parallel kinetic resolution (PKR).[4] In principle, DKR is the simpler approach, but it is limited to systems where interconversion of enantiomers is possible during KR. The more recently recognized alternative of PKR also has limitations, but they are related more to reagent selectivity and experimental design.

In PKR, two kinetic resolutions are performed simultaneously ("in parallel") so that each enantiomer is converted to distinct products via two enantiodivergent pathways.[5] If the two kinetic resolutions convert each enantiomer at a similar rate, then the starting material remains racemic throughout, and the mass action problem is avoided. For the ideal PKR experiment, the two kinetic resolutions should (1) occur with similar rates, (2) use two reagents with

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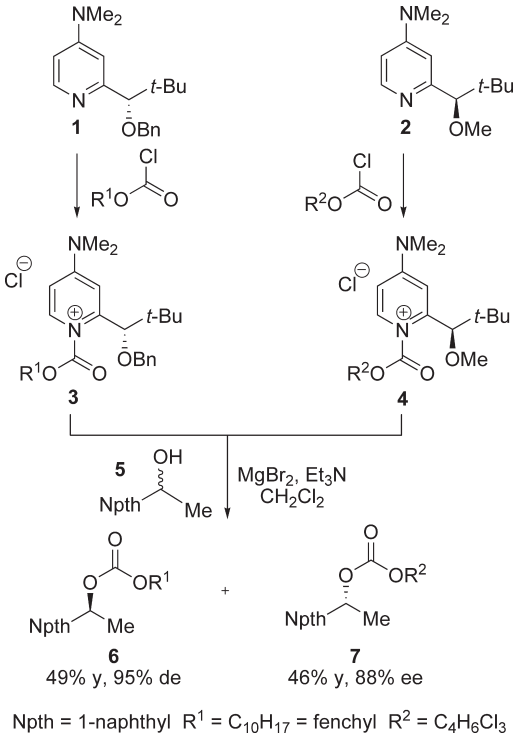
complementary enantioselectivies, (3) take place without mutual interference by the reagents, and (4) afford readily separated products. These requirements involve considerable planning and optimization, but numerous examples of PKR using stoichiometric reagents are now known,[5] including nitrone cycloaddition,[6] Horner−Wadsworth−Emmons (HWE) olefination,[7] Michael addition,[8] reactions of lithiated oxazolidinones,[9] and transesterification.[10]

Alternative approaches are available for converting the enantiomers of a racemic mixture into distinct products using a single chiral reagent or catalyst. Such reactions also involve two enantiodivergent pathways and were cited in the original paper discussing PKR,[4] but they are conceptually distinct and have been termed divergent reactions of a racemic mixture.[11] In contrast to the PKR experiments, single reagent methods do not exploit the relative rates of enantiomer conversion, do not encounter or deal with the mass action problem, and do not benefit from maintaining a 1:1 ratio of enantiomers throughout.[12]

In a representative PKR experiment,[4] racemic alcohol **5** was treated with equimolar amounts of preformed

SCHEME 1. Stoichiometric PKR



Npth = 1-naphthyl $R^1 = C_{10}H_{17}$ = fenchyl $R^2 = C_4H_6Cl_3$

quasi-enantiomeric pyridinium salts **3** and **4** to afford two mixed carbonates **6** and **7** in high yield and enantiomeric excess (Scheme 1). Recovery of carbonate **6** in 49% yield and 95% de corresponds to $s = 125$ in a standard kinetic resolution. Such high selectivity is remarkable considering that classical KR of alcohol **5** using a single chiral pyridinium salt (either **3** or **4**) occurs with $s = 41-42$. However, like nearly all reported PKR experiments,[5−10] the example of Scheme 1 has the disadvantage that it uses stoichiometric chiral reagents.

In principle, PKR is also possible using a combination of two chiral catalysts with two achiral reagents in place of the two stoichiometric chiral reagents. This is a more difficult experiment because requirement (3), above (noninterfering reagents), can only be satisfied if each of the chiral catalysts activates only one of the two achiral reagents with high reagent selectivity. So far, only one study has demonstrated PKR under catalytic conditions, and the necessary reagent selectivity could only be achieved by relying on phase isolation methods.[13] Thus, a soluble, chiral phosphine catalyst *ent*-**8a**[14a] was used in concert with the lipase catalyst ChiroCLEC **9** to derivatize the racemic alcohol **5** (Scheme 2). Because the insoluble lipase has little reagent selectivity and activates a broad range of achiral acyl donors, it was essential to differentiate reagents according to solubility and to design an insoluble acyl donor that would be activated only by the (soluble) phosphine catalyst *ent*-**8a**. The success of this PKR experiment therefore depends on (1) selective activation of soluble vinyl pivalate (**11**) by the insoluble ChiroCLEC (**9**), (2) no reactivity between **11** and phosphine *ent*-**8a**, (3) activation of the insoluble, polymer-supported anhydride **10** by the soluble *ent*-**8a**, and (4) no acyl transfer between the

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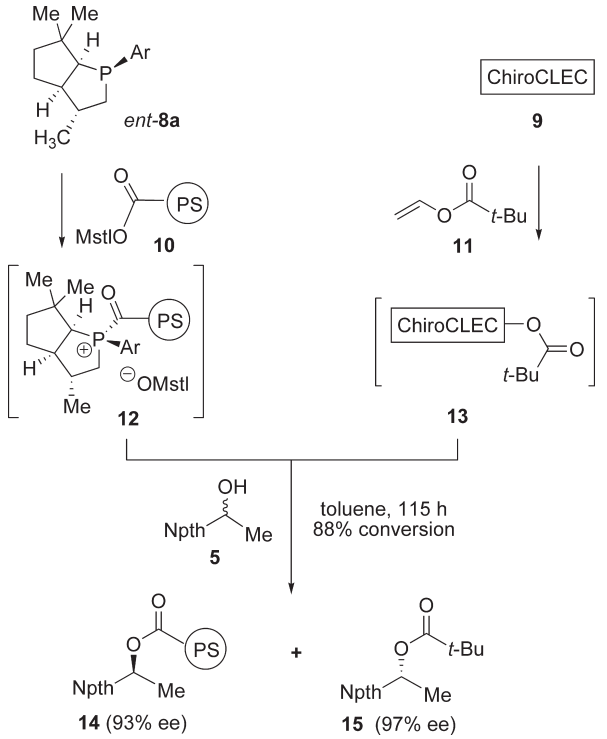
SCHEME 2. Catalytic PKR (Acyl Transfer)



insoluble, activated intermediates **12** and **13** (noninterference). The conditions are satisfied almost perfectly using the three-phase procedure, and the PKR experiment yields the readily separated, enantioenriched esters **14** and **15** (93% ee and 97% ee, respectively). However, these experiments required serious optimization and the results did not come easily.

Fully catalytic PKR using acyl transfer under homogeneous conditions would be more convenient and more scalable, but such an experiment is more challenging. By comparison with the three-phase procedure, homogeneous catalytic PKR confronts a greater risk of interference between quasi-enantiomeric, activated intermediates analogous to **12** and **13** because there is no protection against reversible acyl exchange if all of the reagents are soluble. However, the most difficult problem is to find two catalysts that will selectively activate only one of two soluble, achiral reagents. This becomes especially challenging if the experiment is designed to effect an enantiodivergent derivatization of the racemic substrate using two chiral catalysts that function according to similar mechanistic principles. Below, we describe the demonstration of such an example involving catalytic PKR acylation experiments under homogeneous conditions.

Results and Discussion

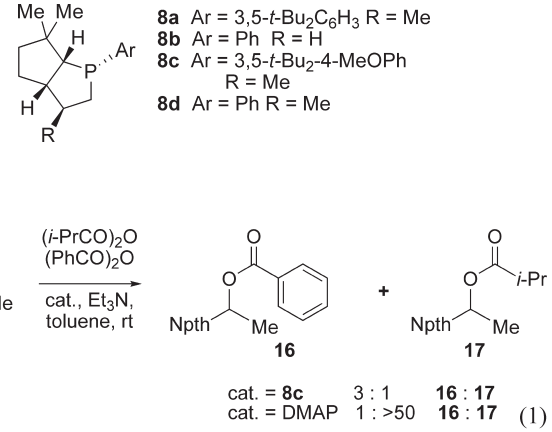
During an investigation of chiral nucleophilic catalysts in the phosphabicyclo[3.3.0]octane (PBO) series (**8a**–**d**),[14] we noticed that phosphines catalyze the benzoylation of alcohols significantly faster than they catalyze the corresponding

TABLE 1. Kinetic Resolution of Alcohol 5 with TADMAP Analogues and $(i\text{PrCO})_2\text{O}$ [a]

entry	cat. (%)	solvent	temp (°C)	time (h)	% conv	*s*
1	**18a** (1%)	toluene	rt	7	40	1.4
2	**18b** (1%)	toluene	rt	92	35	3.4
3	**18b** (1%)	*tert*-amyl alcohol	rt	48	41	5.1
4	**18b** (1%)	*tert*-amyl alcohol	0	48	40	5.3
5	**18c** (1%)	*tert*-amyl alcohol	0	24	52	3.5
6	**18d** (1%)	*tert*-amyl alcohol	0	16	50	2.3
7	**18b** (2%)	3:1 *tert*-amyl alcohol: DCM	−25	37	27	6.1
8	**18b** (4%)	DCM	−25	28	21	3.2

[a] All reactions used [**5**] = 0.1 M in the given solvent with 1−4 mol % of catalyst, 1 equiv of isobutyric anhydride, and 1.1 equiv of Et_3N.

isobutyroylation.[15] Following this lead, we have studied the competition between benzoic anhydride and isobutyric anhydride in the esterification of alcohol **5** using the second-generation catalyst **8c**[14b] (generated in situ from the HBF_4 salt using Et_3N) to activate a mixture of the two anhydrides (1.5 molar equiv each relative to **5**). The rate advantage for benzoylation was reflected in the formation of a 3:1 mixture of the benzoate **16** and the isobutyrate **17** (eq 1). To exploit this result in PKR, the modest 3:1 reagent selectivity of **8c** would have to be improved, and a second catalyst would have to be found that selectively activates the aliphatic anhydride. Initial studies quickly established that isobutyroylation is much faster than benzoylation using *p*-dimethylaminopyridine (DMAP) or its derivatives as catalysts. Indeed, a similar anhydride competition experiment with DMAP + **5** gave the isobutyrate ester **17** as the sole product according to NMR assay (eq 1). Accordingly, we turned to the evaluation of chiral DMAP derivatives[16,17] to find a catalyst having similar enantioselectivity in simple KR compared to **8c**, as well as high anhydride selectivity in competition experiments. These characteristics alone are not sufficient to predict successful PKR, but they provide a simple basis for the evaluation of potential PKR catalysts.



The first-generation chiral DMAP catalyst developed in our laboratory (**18a**, TADMAP) had been optimized for acyl migration applications and does not perform well in the kinetic resolution of **5** (s = 1.4, Table 1, entry 1).[18] In an

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SCHEME 3. Synthesis of TADMAP Analogues

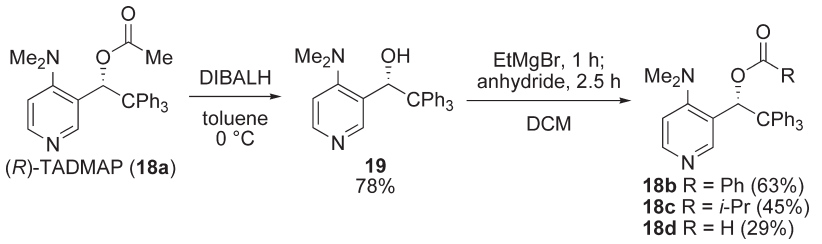


TABLE 2. Simple Kinetic Resolution of 5 and 20a,b Using Catalysts 8c,d and 18b[a]

entry	alcohol	R^1	R^2	cat. (mol %)	anhydride	time (h)	% conv	*s*
1	**5**	1-Npth	Me	**8c** (4%)	nicotinic	3	79	7.5
2	**5**	1-Npth	Me	**8d** (4%)	nicotinic	3	68	11
3	**5**	1-Npth	Me	**18b** (2%)	isobutyric	37	27	6.1
4	**20a**	2-MeC_6H_4	Me	**8d** (2%)	nicotinic[b]	20	37	17
5	**20a**	2-MeC_6H_4	Me	**18b** (2%)	isobutyric[c]	64	50	14
6	**20b**	Ph	*t*-Bu	**8d** (2%)	nicotinic[b]	20	34	57
7	**20b**	Ph	*t*-Bu	**18b** (2%)	isobutyric[c]	64	43	9.9

[a]All reactions were conducted at −25 °C using 1 equiv of alcohol, 1 equiv of anhydride, 1.5 equiv of Et_3N, and 2−4 mol % of catalyst and were diluted to 0.1 M substrate in 3:1 *tert*-amyl alcohol/DCM unless noted. [b]0.6 equiv of anhydride. [c]2.5 equiv of anhydride.

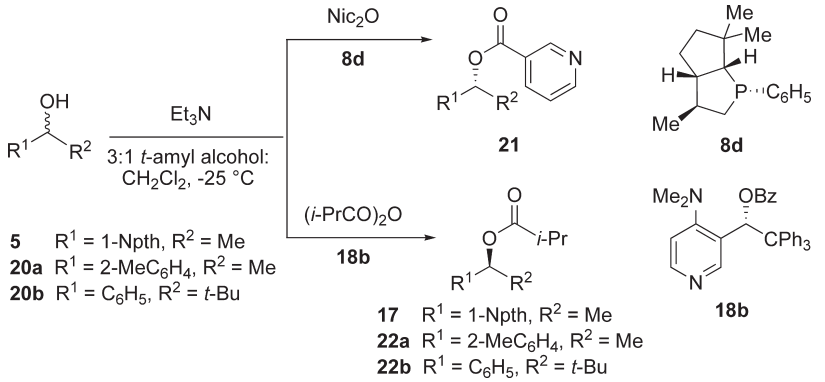
effort to improve enantioselectivity, **18a** was modified by replacement of the acetate by other carboxylates. Enantioenriched **18a** was easily cleaved to the alcohol **19** by reduction, but the hindered **19** was resistant to esterification with anhydrides. Strongly basic conditions were problematic due to facile trityl anion cleavage at the alkoxide stage,[16] but the magnesium alkoxide generated by treating **19** with EtMgBr reacted normally with anhydrides to afford the desired esters **18b**−**d** (Scheme 3). The new esters were screened as catalysts for the kinetic resolution of racemic alcohol **5**, and the benzoate ester **18b** proved to be somewhat more enantioselective (s = 3.4, Table 1, entry 2) compared to **18a**. Enantioselectivity was higher in *tert*-amyl alcohol compared to toluene (entry 3), and a further increase was observed at 0 °C (entry 4). The isobutyrate or formate analogues (**18c**,**d**) were less enantioselective (entries 5 and 6), so benzoate **18b** was selected for detailed optimization. Access to lower temperatures was limited by the freezing point of *tert*-amyl alcohol, but addition of DCM as cosolvent allowed KR at −25 °C, resulting in s = 6.1 (entry 7). The higher s value is due to the temperature, and not the cosolvent (s = 3.2 in DCM; entry 8). This improved level of enantioselectivity for catalyst **18b** in entry 7 was deemed sufficient for proof of principle PKR experiments if the other experimental criteria for PKR could be satisfied.

Although the chiral phosphine **8c** catalyzed the acylation of **5** with complementary anhydride selectivity in favor of Bz_2O over $(i\text{-PrCO})_2O$ compared to **18b**, the ratio of products (**16**/**17** = 3:1) was too low for PKR. Several electron-rich aromatic anhydrides were evaluated but did not improve the results with alcohol **5** using catalyst **8c** in toluene solution. Thus, the competition between isobutyric anhydride vs $(ArCO)_2O$ gave modest product ester ratios (arylcarboxylate vs isobutyrate **17**) as follows: Ar = *p*-methoxyphenyl, 1:1.9; Ar = *m*-methoxyphenyl, 2.7:1; Ar = 3,5-dimethoxyphenyl, 1.5:1). A more promising anhydride selectivity was observed using phosphine catalyst **8c** with the electron-deficient *m*-chlorobenzoic anhydride vs isobutyric anhydride (chlorobenzoate/isobutyrate **17** = 18:1). However, *m*-chlorobenzoic anhydride gave disappointing selectivity in the complementary competition experiment with the DMAP-derived catalyst **18b** (chlorobenzoate/isobutyrate **17** = 1:6). Finally, the competition experiment was repeated using nicotinic anhydride as an electron-deficient analogue of the *m*-chlorobenzoic anhydride. Under the conditions already optimized for simple KR (Table 1, entry 7; *t*-amyl alcohol/DCM at −25 °C), the competition between nicotinic vs isobutyric anhydrides with phosphine **8d** as catalyst afforded only the nicotinate ester. On the other hand, the same anhydride competition using the complementary DMAP-derived catalyst **18b** again gave modest, but opposite anhydride selectivity (nicotinate/**17** = 1:6). The match of complementary anhydride selectivities in the nicotinate experiments was not as close as desired for PKR, but a potential solution to the problem of finding two sets of complementary catalysts and anhydrides appeared to be in hand.

Attention was now turned to optimizing the simple kinetic resolutions of representative racemic alcohol substrates using individual components of potential complementary catalyst/anhydride pairings. Under the best conditions, moderate enantioselectivity factors were found with both the phosphine- and the DMAP-derived catalysts for KR of benzylic alcohols **5**, **20a**, and **20b** (Table 2). The simplest *P*-phenyl catalyst **8d** was more enantioselective than the hindered analogue **8c** in *tert*-amyl alcohol/DCM (entry 2 vs 1), so the other phosphine-catalyzed experiments used **8d**. Good complementarity was found in the acylation experiments with alcohols **5** and **20a**, as judged by similar enantioselectivities with each individual catalyst of the complementary pair. However, alcohol **20b** was a much better substrate for nicotinic anhydride activated by phosphine **8d** compared to the complementary reagent combination of isobutyric anhydride activated by the DMAP-derived **18b** (entries 6 vs 7).

According to the preliminary experiments, phosphine **8d** preferentially converts (*R*)-**5** into the corresponding nicotinic ester **21**, while DMAP derivative **18b** converts the (*S*)-alcohol into isobutyrate **17** (Table 3). These results define

TABLE 3. Parallel Kinetic Resolutions of Alcohols Using Catalysts 8d and 18b[a]

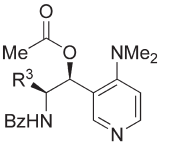


				catalyst (mol %)		ester ratio	nicotinate **21**		butyrates **17**/ **22**	
entry	alcohol	R^1	R^2	**8d**	**18b**	Nic/ *i*Bu	yield (%)	ee (%)	yield (%)	ee (%)
1	**5**	1-Npth	Me	(4.5)	(6.7)	1.6:1.0	62	62	38	−92
2	**5**	1-Npth	Me	(1.3)	(6.7)	1.1:1.0	51	65	46	−73
3	**5**	1-Npth	Me	(1.3)	(6.7)	1.0:1.1[b]	44[b]	68	46[b]	−63
4	**20a**	2-MeC_6H_4	Me	(6.0)	(3.0)	1.2:1.0	52	68	44	−82
5	**20b**	Ph	*t*-Bu	(6.0)	(5.0)	1.0:1.9	33	79	60	−41

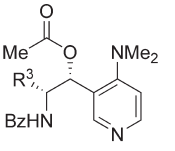
[a]Reactions used 1 equiv of alcohol, 1 equiv of each anhydride, 1.5 equiv of Et_3N, and 0.1 M substrate in 3:1 *tert*-amyl alcohol/DCM unless noted. [b]0.75 equiv of nicotinic anhydride.

two viable complementary kinetic resolutions, so the key PKR experiments were conducted using both anhydrides and both chiral catalysts simultaneously. Catalyst **18b** is considerably less reactive than **8d**, so it was necessary to use a ca. 5:1 ratio of **18b**/**8d** to obtain the ca. 1:1 ratio of products **21** and **17** (entry 2 vs entry 1) as desired for optimal PKR. A further improvement in the product ratio was possible by decreasing the amount of nicotinic anhydride to 0.75 equiv (entry 3). However, these refinements did not result in ideal behavior in the PKR experiments, even though the product ratio was nearly 1:1. Given the enantioselectivities in simple KR (Table 2, entries 2 and 3; $s = 11$ for **21** and $s = 6.1$ for **17**) isobutyrate ester **17** should have been obtained with ca. −72% ee in the experiment of Table 3, entry 3, while nicotinate **21** should be formed with an ee value above ca. 80%. The lower values found for Table 3, entry 3 (−63% ee for **17**; 68% ee for **21**) indicate that one or more of the conditions for PKR was not fully satisfied.

At first glance, it may seem surprising that **17** was obtained with −92% ee in Table 3, entry 1. However, this outcome is not due to a "better" PKR experiment in entry 1. Instead, it is the consequence of the nonideal product ratio (62:38 **21**/**17**) resulting from the greater reactivity of the phosphine catalyst **8d** compared to **18b**. According to Horeau's generalization relating enantiomeric purity with the mol % of products resulting from two divergent reactions starting from a racemic mixture,[19] two products obtained in similar proportions (near 1:1) should have nearly identical ee values. In contrast, if one product is obtained in lower proportion, then its ee value increases compared to the major product. This latter trend is evident in Table 3, where lower ee is observed for the product obtained in higher yield with each of the three substrates (compare entries 3−5). According to the Horeau criterion, entry 3 comes closest to satisfying the requirements for PKR because product yields and ee values are similar. As already mentioned in connection with entry 1, the relatively high ee value for **21** in entry 5 results from the nonideal product ratio.



23a R^3 = *i*-Pr (*S*,*S*)-AcOVaDMAP
23b R^3 = *t*-Bu (*S*,*S*)-AcOLeDMAP



ent-**23a** R^3 = *i*-Pr (*R*,*R*)-AcOVaDMAP
ent-**23b** R^3 = *t*-Bu (*R*,*R*)-AcOLeDMAP

At this stage of our investigation, another generation of chiral DMAP derivatives became available.[20] The catalysts **23a** and **23b** reported earlier were found to activate a mixture of isobutyric and *m*-chlorobenzoic anhydrides with the usual rate advantage for isobutyrate ester formation. However, the faster reacting benzylic alcohol substrate enantiomers proved to have the (*R*)-configuration, the same as for the phosphine catalyst **8d**. To obtain the complementary chiral DMAP catalysts, the published routes were repeated starting from the enantiomeric valinol and *tert*-leucinol, affording *ent*-**23a** and *ent*-**23b**, respectively. Standard evaluations were carried out, and both *ent*-**23a** and *ent*-**23b** were found to have promising enantioselectivity and the expected preference for the (*S*) enantiomer of **5**, but most of the preliminary studies used catalysts **23a** and **23b** prepared from the relatively inexpensive L-*tert*-leucinol.

At room temperature, KR of alcohol **5** using the valine-derived **23a** with isobutyric anhydride was more enantioselective in toluene ($s = 6.8$)[18] than in *tert*-amyl alcohol ($s = 2.7$; Table 4, entries 1 and 2). The more hindered *tert*-leucine-derived **23b** gave somewhat better results in toluene ($s = 8.9$,

(19) Guette, J. P.; Horeau, A. *Bull. Soc. Chim. Fr.* **1967**, 1747.

(20) Duffey, T. A.; Shaw, S. A.; Vedejs., E. *J. Am. Chem. Soc.* **2009**, *131*, 14.

entry 3),[18] and selectivity increased to synthetically useful levels in the temperature range from −40 to −70 °C (s = 20−29, entries 4 and 5). At the lower end of this range, the rate of acylation decreased dramatically, so further experiments were conducted at −40 °C. Alcohol **20a** was also isobutyroylated with moderate enantioselectivity (entry 6), but the more hindered *tert*-butyl-substituted alcohol **20b** reacted with minimal enantiomer discrimination (entry 7; s = 1.8).

Given the promising enantioselectivity in simple KR using the DMAP-derived catalysts **23a** and **23b**, the anhydride selectivity was tested in the usual competition experiments with isobutyric vs *m*-chlorobenzoic or nicotinic anhydrides. Formation of the isobutyrate over the *m*-chlorobenzoate or nicotinate esters was favored by ratios of 16:1 and 11:1, respectively, using **23a** (toluene, rt). These selectivities are significantly improved compared to the corresponding values observed using **18b**, but the best KR results with catalyst **23b** were obtained in toluene, while prior experiments with **18b** and the phosphine catalyst **8d** had been conducted in *tert*-amyl alcohol. Fortunately, simple KR of alcohol **5** with *m*-chlorobenzoic anhydride activated by **8d** proved to be even more enantioselective in toluene (s = 19.8, −40 °C). These observations quickly displaced nicotinic anhydride as a reagent of interest and established *m*-chlorobenzoic anhydride as a viable alternative for PKR experiments.

With similar and complementary enantioselectivities as well as anhydride selectivities demonstrated for *ent*-**23b** vs phosphine catalyst **8d**, the new catalyst combination was evaluated for PKR of alcohol **5**. In contrast to **18b**, *ent*-**23b** was more reactive than **8d**, and it was necessary to increase the proportion of **8d** to equalize the rates for conversion of each enantiomer. Using a 2.2:1 ratio of **8d**/*ent*-**23b**, a 1:1.2 ratio of *m*-chlorobenzoate **24** to isobutyrate **17** was obtained (ca. 92% conversion after 3 h; Table 5, entry 1). After isolation and saponification of the esters, the alcohols were assayed by HPLC on chiral support. The alcohol derived from *m*-chlorobenzoate **24** was obtained in 88% ee and the alcohol from isobutyrate **17** in −75% ee.

The unreacted alcohol recovered from the above experiment was found to have 27% ee, indicating that one of the enantiomers had been consumed faster than the other. To compensate, the ratio of **8d**/*ent*-**23b** was increased to 2.6:1, and afforded the ideal 1:1 ratio of products (NMR assay). However, this did not significantly alter the product ee, even though the unreacted alcohol (−8% ee) was closer to the desired 0% ee for an ideal PKR experiment (entry 2). Doubling the catalyst loading resulted in a small increase in isobutyrate ee (**17**; −78% ee) at the expense of *m*-chlorobenzoate ee (**24**; 86%; entry 3), but unreacted alcohol **5** recovered from this experiment was obtained with a nonideal value of 19% ee (0% ee is ideal). All of the PKR experiments in Table 5 generated **8d** in situ from the HBF_4 salt as precatalyst via deprotonation with Et_3N. This procedure provides better control of catalyst loading and minimizes the risk of phosphine oxidation to the catalytically inactive phosphine oxide.[14b,21] Despite these precautions, the unexpected variations in recovered alcohol ee could not be suppressed, and the contrast with the relatively consistent product ester ee values could not be explained.

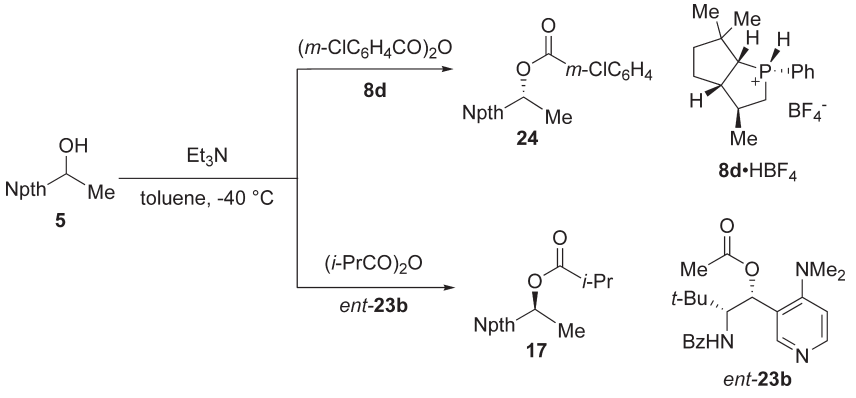
Under ideal PKR conditions, the product corresponding to simple KR with s = 20 should be obtained with 90% ee (calculated ee at <1% conversion in simple KR), so the recovery of *m*-chlorobenzoate ester **24** with 86−88% ee is near-optimal. If the corresponding simple KR experiment were taken to 50% conversion, then **24** would be formed with 79% ee, indicating that PKR has significantly enhanced

TABLE 4. KR of Alcohols with Isobutyric Anhydride Using 23a,b[a]

entry	alcohol	R^1	R^2	catalyst	solvent	temp (°C)	s
1	**5**	1-Npth	Me	**23a**	*tert*-amyl alcohol	rt	2.7
2	**5**	1-Npth	Me	**23a**	toluene	rt	6.8
3	**5**	1-Npth	Me	**23b**	toluene	rt	8.9
4	**5**	1-Npth	Me	**23b**	toluene	−40	20.5
5[b]	**5**	1-Npth	Me	**23b**	toluene	−70	29
6	**20a**	2-MeC_6H_4	Me	**23b**	toluene	−40	9.5
7	**20b**	Ph	*t*-Bu	**23b**	toluene	−40	1.8

[a]All reactions used 1 equiv of alcohol, 1 equiv of isobutyric anhydride, 1.5 equiv of Et_3N, 1 mol % of catalyst, 0.06 M substrate, 4 h; catalyst **23a,b** consistently gave the *R* ester. [b]8 h reaction time.

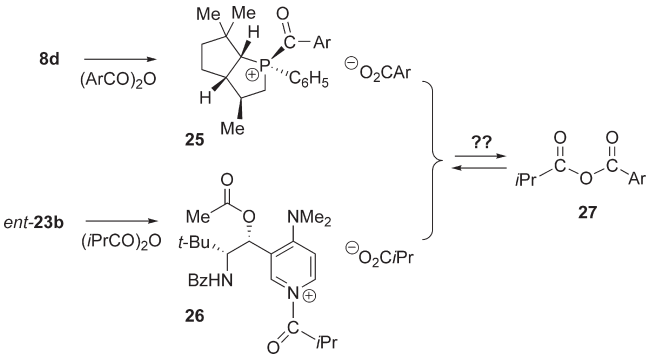
TABLE 5. Parallel Kinetic Resolutions of Alcohols with Catalysts 8d and *ent*-23b[a]



entry	**8d** (mol %)	*ent*-**23b** (mol %)	time (h)	ratio **24**/**17**/**5**[b]	**24** (% ee)	**17** (% ee)	**5** (% ee)
1	2.2	1	3	1.0:1.2:0.18	88	−75	27
2	2.6	1	3	1.0:1.0:0.5	87[c]	−76[d]	−8
3	5.2	2	2	1.0:1.2:0.53	86	−78	19

[a]All reactions used 1 equiv of **5**, 1 equiv of each anhydride, 1.5 equiv of Et_3N, and 1−5.2 mol % of each catalyst and were diluted to 0.06 M substrate in toluene. [b]By NMR assay. [c]44% isolated. [d]33% isolated.

SCHEME 4. Intermediates in Catalyzed Acyl Transfer



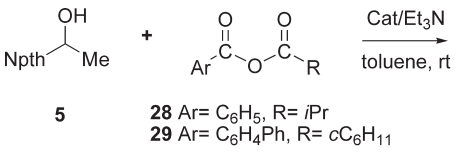
enantiomeric purity. However, the ideal PKR conditions were not fully satisfied because **17** was obtained with −75 to −78% ee, lower than the expected −90% ee and essentially the same as the value predicted from simple KR at 50% conversion (s = 20.5). Furthermore, recovery of alcohol **5** with significant ee indicates that at least one of the PKR prerequisites had not been fully controlled.

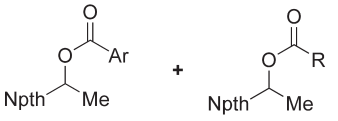
In the PKR experiments of Table 5, the *m*-chlorobenzoate **24** was obtained in nearly ideal enantiomeric excess, suggesting that the formation of **24** occurs cleanly by the intended phosphine catalysis resulting from activation of *m*-chlorobenzoic anhydride as desired. If this deduction is correct, then problems in the isobutyric anhydride activation pathway could be responsible for the observed nonideal behavior, but it was difficult to imagine how one of two mechanistically similar pathways might become compromised without affecting the other pathway. On the other hand, there was no mystery regarding the most delicate stage of the process where reagent interference might occur. The anhydride activation stage leading to ion-pair intermediates **25** and **26** was the likely culprit (Scheme 4) because two different carboxylate anions must be present simultaneously. In principle, this would allow carboxylate exchange between the ion pairs **25** and **26** and would open the door to reversible acyl transfer, equilibration, and formation of the mixed anhydride **27**. Indeed, a simple NMR control experiment in benzene established that both DMAP and phosphine **8d** promote the scrambling of a 1:1 mixture of benzoic and isobutyric anhydrides to form a statistical mixture of the mixed and symmetrical anhydrides within ca. 1 h at room temperature. Initially, we saw no harm in anhydride scrambling and even considered the possibility that mixed anhydrides such as **27** or **28** may be sufficient reagents for PKR if selective activation of the two different acyl groups would occur with the same selectivity as observed in competition experiments with the symmetrical anhydrides. However, our attempts to probe this possibility encountered a very different scenario.

Early experiments with mixed anhydrides tested **28**, generated from sodium benzoate and isobutyroyl chloride. As expected, the presumed *internal* competition for acyl activation with DMAP as catalyst gave the same preference for the aliphatic (isobutyrate) ester **17** (Table 6, entry 1) as observed under conditions of intermolecular competition using the symmetrical anhydrides (eq 1). However, the corresponding

(21) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

TABLE 6. Mixed Anhydride Activation[a]





entry	cat. (mol %)	Ar	R	product ratio
1	DMAP (20)	Ph	*i*-Pr	1:50 **16**/**17**
2	**8c** (1)[b]	Ph	*i*-Pr	1:3 **16**/**17**
3	**8d** (5)[b]	biphenyl	cyclohexyl	1:4 **30**/**31**
4	**18b** (5)	biphenyl	cyclohexyl	1:50 **30**/**31**

[a]All reactions used 1 equiv of **5**, 1−2 equiv of each anhydride (1:1 ratio), and 1.5 equiv of Et_3N and were diluted to 0.2 M substrate in toluene at room temperature. [b]The phosphine was generated in situ from the HBF_4 salt; an additional 0.1 equiv of Et_3N was added.

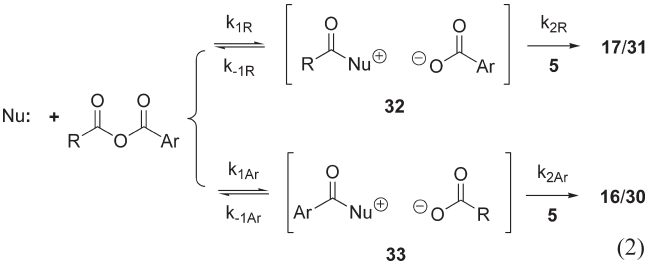
internal competition experiment with phosphine **8c** as catalyst gave the *same isobutyrate 17 as the major product*, in striking contrast to the result of eq 1. At first, we suspected that this outcome might be an artifact resulting from intervention by contaminants in the mixed anhydride **28** (ca. 5% of isobutyric anhydride was present). Accordingly, a search was launched to find a crystalline mixed aryl-aliphatic anhydride that might be obtained in better purity, and this search lead to the mixed anhydride **29**. To minimize the possibility of contamination, **29** was used immediately upon crystallization, and was tested with the "real" catalysts **8d** and **18b** (Table 6, entries 3 and 4). Once again, the aliphatic (cyclohexanecarboxylate) ester was the major product with both the phosphine- and the DMAP-based catalysts.

The evidence discussed above indicates that formation of mixed anhydride **27** is likely during the PKR experiments. This would be detrimental to enantiomeric excess of the isobutyrate product **17** because an additional fraction of **17** would be formed as the minor enantiomer due to the activation of **27** by the phosphine catalyst. If this undesired pathway is responsible for the formation of ca. 8% of the isobutyrate ester **17** in Table 5, then all of the observed deviations from ideal PKR behavior with catalyst **8d** can be attributed to mixed anhydride formation. Analogous deviations are not observed in the *m*-chlorobenzoate product **16** because mixed anhydride activation by the DMAP-derived *ent*-**23b** follows the same pattern of acyl discrimination as with the symmetrical anhydrides.

The origins of complementary anhydride selectivity for the phosphine vs the DMAP-derived catalysts remain to be considered. Nucleophiles activate anhydrides by forming ion pairs (**32** or **33**, eq 2), and the rate of acylation depends on $K_{eq} = k_1/k_{-1}$ (extent of ion pair formation) and also on k_2 (ion pair reactivity).[22] For the phosphine catalysts,

(22) (a) Heinrich, M. R.; Klisa, H. S.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4826. (b) Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem.—Eur. J.* **2005**, *11*, 4751. (c) Held, I.; Villinger, A.; Zipse, H. *Synthesis* **2005**, *9*, 1425. (d) Fischer, C. B.; Xu, S.; Zipse, H. *Chem.—Eur. J.* **2006**, *12*, 5779.

anhydride selectivity increases as the leaving group ability of the carboxylate anion increases. This trend is evident in the improved intermolecular competition using benzoic, *m*-chlorobenzoic, and nicotinic anhydrides vs isobutyric anhydride as discussed previously, and it is also apparent in the mixed anhydride experiments. Two ion pairs **32** and **33** are possible (Nu: = phosphine) in experiments using mixed anhydrides, and preferential formation of the aliphatic ester **17** indicates that product formation via ion pair **32** is favored over ion pair **33**. A comparison of the favored ion pair **32** from the mixed anhydrides with the favored ion pair **25** from the two symmetrical anhydrides in phosphine-catalyzed acylation reveals that the common element is the arylcarboxylate leaving group. Since this is the more stable carboxylate anion, preferential formation of **17** can be attributed to an increase in the value of k_{1R}/k_{-1R} for the equilibrium with **32** compared to the analogous term k_{1Ar}/k_{-1Ar} in the competing pathway via **33**.



(2)

A similar analysis of the DMAP-catalyzed acyl transfer reactions leads to a different conclusion. Since DMAP derivatives selectively catalyze the isobutyroylation of alcohols regardless of the isobutyroyl donor anhydride, ion pairs **26** and **32** are the dominant isobutyroylating agents. The common element between **26** and **32** is an acylated pyridinium ion, while the carboxylate anions are different. In this scenario, selectivity for the DMAP catalysts is determined more by the relative reactivity of the intermediate ion pairs (as in **32** vs **33**) and the corresponding values of k_{2R} (isobutyroylation) compared to k_{2Ar} (aroylation). We do not have sufficient evidence to comment in detail on the factors that would favor k_{2R} vs k_{2Ar} for the DMAP-derived catalysts, but a simple rationale can be invoked that is consistent with the data. Somewhat increased delocalization is expected for the *N*-aroylpyridinium subunit in the ion pair **33** vs **32** (Nu: = DMAP), a factor that would decrease k_{2Ar} and would result in a slower aroylation compared to isobutyroylation. The lower anhydride selectivity (aromatic vs isobutyric) for DMAP-derived catalysts with the relatively electron poor aromatic anhydrides (nicotinic, *m*-chlorobenzoic) compared to electron-rich aromatic anhydrides discussed earlier supports this rationale. As the π-electron donor ability of Ar decreases, the *N*-aroylpyridinium intermediate **33** (Nu = DMAP) has a smaller advantage compared to **32** (Nu = DMAP).

In principle, the reversed anhydride selectivity for the phosphine catalysts with the symmetrical anhydrides may also reflect a contribution from steric effects[22d] that might decrease k_{2R} for the isobutyroylations relative to k_{2Ar} for the competing aroylations. Although mechanistic details for the acyl transfer stage remain uncertain, pathways from **25** involving a conventional tetrahedral intermediate, the analogous transition state, or the related phosphoranes can be considered. All of these species could play a role, but some version of carboxylate-assisted nucleophilic attack by the alcohol substrate at the carbonyl group of ion pair **25** is necessary. This event would be resisted by C sp^3 vs P sp^3 repulsions between the quaternary phosphorus and the developing quaternary character at the isobutyroyl C=O carbon regardless of mechanistic details. In contrast, the analogous event in DMAP-derived intermediates such as **26** would involve a less demanding C sp^3 vs N sp^2 repulsion. The simplest version of the steric argument is not consistent with the mixed anhydride experiments because the aliphatic (isobutyrate) ester is favored with phosphine as well as DMAP catalysts. On the other hand, no simple argument can address the role of carboxylate anions on k_{2R} vs k_{2Ar} at the current stage of mechanistic understanding. Certainly, the anions are important for enantioselectivity,[23] and it would be premature to assume that their contributions to the relative rate terms would follow a simple pattern.

Summary

We have presented several proof of principle examples of fully catalytic parallel kinetic resolution under homogeneous conditions. These experiments show that it is possible to use complementary chiral catalysts for the selective activation of two different achiral acyl donors in solution, resulting in the formation of distinct enantioenriched esters. The best experiments involve the simultaneous, selective generation of activated ion pair intermediates **25** and **26** from a mixture of isobutyric and *m*-chlorobenzoic anhydrides. Although complementary anhydride selectivity by the catalysts **8d** and *ent*-**23b** is compromised by minor formation of the undesired mixed anhydride **27**, it is clear that the quasi-enantiomeric[24] intermediates **25** and **26** discriminate quite well between alcohol substrate enantiomers. Near-ideal enantiomeric excess was observed for (*R*)-**24**, the product of enantioselective aroylation in the PKR experiment. However, the complementary process leading to the isobutyrate (*S*)-**17** encountered interference by a second (minor) pathway, the activation of mixed anhydride **27** by phosphine **8d**. This undesired pathway generates ion pair **32** (Nu: = **8d**), an intermediate that functions as the quasi-enantiomer of **26** and is responsible for increased product contamination by the enantiomer (*R*)-**17**.

Further studies will be needed to control the behavior of mixed acyl transfer agents analogous to **27** or to develop methods that use more robust and more compatible activated intermediates compared to **25** and **26**. Many options can be considered for this purpose. One possibility would be to develop acyl donors having more stabilized anionic leaving groups in place of the carboxylate anions to minimize

(23) In one of our attempts to avoid the problem of mixed anhydride formation, we considered using two activated esters having the same anionic leaving group attached to different acyl groups. The *N*-isobutyroyl and *N*-benzoyl derivatives of 4-phenyltetrazole were evaluated for this purpose. Each tetrazolide was activated for the usual esterifications of **5** by the DMAP-derived catalyst **18b** and the phosphine **8d**, respectively, in 3:1 *tert*-amyl alcohol/DCM at −25 °C. However, **8d** gave $s = 2.5$ for the benzoylation, while **18b** afforded racemic products ($s = 1$) in the isobutyroylation. These experiments hint at the variety of options that may be considered for improving PKR, but they caution against simple assumptions regarding the role of anions in the product-determining step for acyl-transfer experiments.

(24) For a recent discussion of relevant concepts and terminology, see: Zhang, Q.; Curran, D. P. *Chem.—Eur. J.* **2005**, *11*, 4866.

nucleophile-induced mixed anhydride formation.[23] Another alternative would be to design PKR experiments where one of the parallel KR pathways is mechanistically different. Our first proof of principle examples were chosen to tackle the most difficult scenario involving parallel, mechanistically similar pathways where reagent compatibility can be compromised by acyl exchange between ion pairs **25** and **26**. Future versions of fully catalytic PKR might improve reagent compatibility by replacing one of the two parallel acylations with an enantiodivergent process that incorporates distinct functionality.

Experimental Section

Et_2O, THF and CH_2Cl_2 (DCM) were dried by passing through a column of activated alumina. Ethyl acetate and Et_3N were distilled over CaH_2, Et_2NH was distilled over KOH, and *tert*-amyl alcohol was carefully distilled over molten sodium. Solvents used for reactions involving phosphines were further deoxygenated by bubbling a stream of N_2 through the solvent (~30 min) prior to use. Organolithium reagents were titrated with diphenylacetic acid in THF. All other reagents were used as received from the manufacturer. Analytical thin layer chromatography (TLC) was done using 0.25 mm K6F silica gel 60 Å plates. Flash chromatography followed the Still procedure[25] using silica gel/Puracil 60 Å (230−400 mesh). All reactions were performed under an atmosphere of nitrogen in oven-dried glassware. Catalysts **23a** and **23b** were prepared as previously described,[20] and the same route was used to prepare the previously unreported enantiomeric catalysts *ent*-**23a** and *ent*-**23b** from (*R*)-*N*-benzoylvalinol and (*R*)-*N*-benzoyl-*tert*-leucinol, respectively. Catalysts *ent*-**23a**,**b** were purified by recrystallization (>98% dr, NMR assay) as previously described for **23a**,**b**. As expected, the NMR data for *ent*-**23a**,**b** are identical to those reported previously for **23a**,**b**.[20] Nicotinic anhydride and *m*-chlorobenzoic anhydride were prepared according to prior literature.[28,29]

1-(4-Dimethylaminopyridin-3-yl)-2,2,2-triphenylethanol (19). To a solution of (*R*)-TADMAP (**18a**)[16] (175 mg, 0.41 mmol, 96.4% ee) in toluene (4.1 mL) cooled to 0 °C was added DIBAL (0.89 mL, 1 M solution in toluene) via syringe. The mixture was stirred at 0 °C for 2 h and then quenched with aqueous sodium potassium tartrate (satd, 4 mL) and stirred vigorously for 2 h to break up the emulsion. An additional 2 mL of saturated aqueous sodium potassium tartrate was added along with EtOAc (10 mL) and 10% HCl (0.5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), and the aqueous later was extracted with EtOAc (10 mL). All aqueous layers were combined and extracted with DCM (2 × 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated (aspirator) to give 123 mg (78%) of a white solid (**19**) that was used in the subsequent reaction without further purification: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.26 (1H, d, J= 5.3 Hz) 7.56 (1H, s) 7.38−7.33 (6H, m) 7.27−7.16 (9H, m) 6.88 (1H, d, J = 5.4 Hz) 6.75 (1H, s) 5.17 (1H, br s) 2.55 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 160.4, 151.1, 149.3, 144.5, 130.6, 129.9, 127.7, 126.4, 115.0, 73.1, 64.8, 44.5.

Representative Procedure for the Synthesis of TADMAP Derivatives: Benzoic Acid 1-(4-Dimethylaminopyridin-3-yl)-2,2,2-triphenylethyl Ester (18b). Alcohol **19** (121 mg, 0.31 mmol) was dissolved in DCM (1.5 mL). The solution was cooled to 0 °C, and EtMgBr (0.85 M in Et_2O, 0.54 mL, 0.46 mmol) was added via syringe. The cooling bath was removed, and the mixture was stirred for 1 h at rt. The mixture was recooled to 0 °C, and benzoic anhydride (208 mg, 0.92 mmol) was added as a solution in DCM (0.4 mL) via syringe. The solution immediately turned yellow, was stirred for 5 min, and was warmed to room temperature. The mixture was then stirred for an additional 2.5 h, and the solution turned orange. The reaction was quenched with H_2O (1 mL) followed by the addition of $NaHCO_3$ (satd, 10 mL) and extracted with DCM (4 × 10 mL). The combined organic layers were washed with $NaHCO_3$ (satd, 10 mL), dried ($MgSO_4$), and concentrated (aspirator). The crude product was purified by flash chromatography (3 × 14 cm) using 4:1 EtOAc/hexanes with a 1% Et_3N buffer as eluent and collecting 9 mL fractions. Impurities eluted in fractions 6−9. Fractions 10−17 were combined to yield 97 mg (63%) of **18b**, a pale yellow foam. HPLC assay was carried out on a Chiralpak AD analytical column, 5% isopropanol/hexanes, 1 mL/min flow rate. Retention times of enantiomers: 11.1 min (*S*), 20.0 min (*R*), 95% ee; HRMS calcd for $C_{34}H_{30}N_2O_2$ [M + H]; ESMS m/z = 499.2386, found 499.2363; IR (neat, cm^{-1}) 1715, C=O; 1585, C=N; 1265, CO; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.17 (1H, d, J = 5.9 Hz) 8.01 (1H, s) 7.88 (2H, d, J = 7.3 Hz) 7.51 (1H, t, J = 7.6 Hz) 7.40−7.34 (9H, m) 7.26−7.16 (9H, m) 6.73 (1H, d, J = 5.4 Hz) 2.79 (6H, s); ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ 166.2, 159.5, 152.7, 149.9, 143.5, 133.4, 131.1, 130.3, 129.9, 128.7, 126.8, 126.5, 114.3, 73.1, 64.8, 43.8, 27.5.

Isobutyric Acid 1-(4-Dimethylaminopyridin-3-yl)-2,2,2-triphenylethyl Ester (18c). Following the representative procedure for the synthesis of TADMAP derivatives, alcohol **19** (26 mg, 0.066 mmol) was protected as the isobutyrate ester **18c** (8 mg, 29%) at 55% conversion using isobutyric anhydride (31 μL, 0.19 mmol): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.16 (1H, d, J = 5.4 Hz) 7.70 (1H, s) 7.34 (1H, s) 7.30−7.27 (6H, m) 7.23−7.17 (9H, m) 6.71 (1H, d, J = 5.4 Hz) 2.74 (6 H, s) 2.45 (1H, qq, J = 7.3, 6.8 Hz) 0.99 (1H, d, J = 6.8 Hz) 0.96 (1H, d, J = 7.3 Hz).

Formic Acid 1-(4-Dimethylaminopyridin-3-yl)-2,2,2-triphenylethyl Ester (18d). Following the representative procedure for the synthesis of TADMAP derivatives, alcohol **19** (24 mg, 0.062 mmol) was protected as the formate ester **18d** (13 mg, 45%) at 56% conversion using formyl pivaloyl mixed anhydride (17 μL, 0.19 mmol): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.21 (1H, d, J = 6.1 Hz) 8.01 (1H, s) 7.84 (1H, s) 7.47 (1H, s) 7.31−7.27 (6H, m) 7.24−7.19 (9H, m) 6.74 (1H, d, J = 6.1 Hz) 2.68 (6 H, s).

General Procedure for Kinetic Resolutions Using DMAP Derivatives (A): Kinetic Resolution of 5 Using 18b. A solution of alcohol **5** (17 mg, 0.1 mmol), **18b** (0.5 mg, 0.001 mmol, 91% ee), and Et_3N (15 μL, 0.1 mmol) in toluene (0.8 mL) was treated with isobutyric anhydride (17 μL, 0.1 mmol). The reaction was monitored by TLC to an estimated 50% conversion and then was quenched by addition of *i*-$PrNH_2$ (0.1 mL). The mixture was concentrated (aspirator) and purified by flash chromatography. Ester fractions were concentrated, and 5% NaOH/MeOH (1 mL) was added to saponify the ester prior to assay. The solution was warmed gently for 5 min and then left at room temperature for 2 h. Methanol was evaporated, and the residue was filtered through an 8 cm ×1.2 cm pad of silica gel in DCM. After solvent removal (aspirator), HPLC assay was carried out on a chiral support. Conversion and selectivity of the kinetic resolution were calculated by a best fit method using both the ee of the recovered alcohol and ee of the hydrolyzed ester, correcting for the ee of the catalyst.[26]

General Procedure for Kinetic Resolutions Using Phosphine Derivatives (B): Kinetic Resolution of 5 Using 8c. A solution of alcohol **5** (17 mg, 0.1 mmol) and nicotinic anhydride (23 mg, 0.01 mmol) in *tert*-amyl alcohol (0.5 mL) and DCM (0.25 mL) was cooled to −25 °C in a Cryocool. To the mixture was added

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a solution of **8c**·HBF_4 (2 mg, 0.004 mmol) and Et_3N (22 μL, 0.15 mmol) in *tert*-amyl alcohol (0.25 mL). The reaction was stirred for 3 h and then was quenched by addition of *i*-$PrNH_2$ (0.15 mL). The mixture was concentrated (aspirator) and purified by flash chromatography. Ester fractions were concentrated, and 5% NaOH/MeOH (1 mL) was added to saponify the ester prior to assay. The solution was warmed gently for 5 min and then left at room temperature for 2 h. Methanol was evaporated, and the residue was filtered through an 8 cm × 1.2 cm pad of silica gel in DCM. After solvent removal (aspirator), HPLC assay was carried out on a chiral support. Conversion and selectivity of the kinetic resolution were calculated by a best fit method using both the ee of the recovered alcohol and ee of the hydrolyzed ester, correcting for the ee of the catalyst.[26]

Table 1, Entry 2: Isobutyroylation of 5 with 18b. Following the general procedure A, racemic **5** (17 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol), and catalyst **18b** (0.5 mg, 0.001 mmol, 91% ee) in toluene were stirred at rt for 92 h to afford unreacted alcohol *R*-**5** 22.3% ee and isobutyrate *S*-**17** 40.7% ee (after hydrolysis); $s = 3.4$[26] and $c = 35\%$. HPLC analysis: CHIRALCEL OD analytical column, 10% 2-propanol/hexanes, 1 mL/min flow rate. Retention times 9.8 min (*S*), according to (−) sign of optical rotation,[27] 15.0 min (*R*).

Table 1, Entry 3: Isobutyroylation of 5 with 18b. Following the general procedure A, racemic **5** (17 mg, 0.1 mmol), isobutyric anhydride (12 μL, 0.06 mmol), and catalyst **18b** (0.5 mg, 0.001 mmol, 91% ee) in *tert*-amyl alcohol were stirred at rt for 48 h to afford unreacted alcohol *R*-**5** 34.0% ee and isobutyrate *S*-**17** 49.8% ee (after hydrolysis); $s = 5.1$[26] and $c = 41\%$.

Table 1, Entry 4: Isobutyroylation of 5 with 18b. Following the general procedure A, racemic **5** (17 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol), and catalyst **18b** (0.5 mg, 0.001 mmol, 91% ee) in *tert*-amyl alcohol were stirred at 0 °C for 48 h to afford unreacted alcohol *R*-**5** 33.4% ee and isobutyrate *S*-**17** 51.1% ee (after hydrolysis); $s = 5.3$[26] and $c = 40\%$.

Table 1, Entry 5: Isobutyroylation of 5 with 18c. Following the general procedure A, racemic **5** (17 mg, 0.1 mmol), isobutyric anhydride (12 μL, 0.06 mmol), and catalyst **18c** (0.5 mg, 0.001 mmol, 93% ee) in *tert*-amyl alcohol were stirred at 0 °C for 24 h to afford unreacted alcohol *R*-**5** 40.0% ee and isobutyrate *S*-**17** 36.8% ee (after hydrolysis); $s = 3.5$[26] and $c = 52\%$.

Table 1, Entry 6: Isobutyroylation of 5 with 18d. Following the general procedure A, racemic **5** (18 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol), and catalyst **18d** (0.1 mL, 0.01 M in *tert*-amyl alcohol, 0.001 mmol, 95.5% ee) in *tert*-amyl alcohol were stirred at 0 °C for 16 h to afford unreacted alcohol *R*-**5** 27.0% ee, and isobutyrate *S*-**17** 26.7% ee (after hydrolysis); $s = 2.3$[26]and $c = 50\%$.

Table 1, Entry 7: Isobutyroylation of 5 with 18b. Following the general procedure A, racemic **5** (17.2 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol), and catalyst **18b** (0.9 mg, 0.002 mmol, 95% ee) in 3:1 *tert*-amyl alcohol/DCM were stirred at −25 °C for 37 h to afford unreacted alcohol *R*-**5** 24.0% ee and isobutyrate *S*-**17** 66.0% ee (after hydrolysis); $s = 6.1$[26] and $c = 27\%$.

Table 1, Entry 8: Isobutyroylation of 5 with 18b. Following the general procedure A, racemic **5** (17.2 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol), and catalyst **18b** (2 mg, 0.004 mmol, 95% ee) in DCM were stirred at −25 °C for 28 h to afford unreacted alcohol *R*-**5** 11.2% ee, and isobutyrate *S*-**17** 48.0% ee (after hydrolysis); $s = 3.2$[26] and $c = 21\%$.

Table 2, Entry 1: Nicotinoylation of 5 with 8c. Following the general procedure B, racemic **5** (17 mg, 0.1 mmol), nicotinic anhydride (23 mg, 0.1 mmol), and catalyst **8c**·HBF_4 (1 mg, 0.004 mmol) in 3:1 *tert*-amyl alcohol/DCM were stirred at rt for 3 h to afford unreacted alcohol *S*-**5** 99.3% ee, and nicotinate *R*-**21** 40.7% ee (after hydrolysis); $s = 7.5$ and $c = 79\%$. For **21** (R^1= 1-naphthyl, R^2= Me): HRMS calcd for $C_{18}H_{15}NNaO_2$ [M + Na]; ESMS m/z = 300.0995, found 300.0997; IR (neat, cm^{-1}) 1717, C=O; 1590, C=N; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.32 (1H, d, J = 2.2 Hz) 8.78 (1H, dd, J = 4.7, 1.5 Hz) 8.34 (1H, dt, J = 8.1, 2.2 Hz) 8.19 (1H, d, J = 8.8 Hz) 7.92−7.82 (2H, m) 7.70 (1H, d, J = 6.5 Hz) 7.6−7.47 (3H, m) 7.41−7.36 (1H, m) 6.92 (1H, q, J = 6.6 Hz) 1.9 (3H, d, J = 6.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 164.5, 153.4, 151.0, 137.1, 137.0, 133.9, 130.2, 129.0, 128.7, 126.5, 126.3, 125.7, 125.3, 123.5, 123.3, 123.0, 70.9, 21.8.

Table 2, Entry 2: Nicotinoylation of 5 with 8d. Following the general procedure B, racemic **5** (17 mg, 0.1 mmol), nicotinic anhydride (23 mg, 0.1 mmol), and catalyst **8d** (0.004 mg, 0.004 mmol added as a solution of the free phosphine) in 3:1 *tert*-amyl alcohol/DCM were stirred at rt for 3 h to afford unreacted alcohol *S*-**5** 97.5% ee and nicotinate *R*-**21** 46.4% ee (after hydrolysis); $s = 11$ and $c = 68\%$.

Table 2, Entry 3: Isobutyroylation of 5 with 18b. Following the general procedure B, racemic **5** (17.2 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol), and catalyst **18b** (0.9 mg, 0.002 mmol, 95% ee) in 3:1 *tert*-amyl alcohol/DCM were stirred at −25 °C for 37 h to afford unreacted alcohol *R*-**5** 24.0% ee and isobutyrate *S*-**17** 66.0% ee (after hydrolysis); $s = 6.1$[26] and $c = 27\%$.

Table 2, Entry 4: Nicotinoylation of 20a with 8d. Following the general procedure B, racemic **20a** (14 μL, 0.1 mmol), nicotinic anhydride (13 mg, 0.06 mmol), and catalyst **8d** (0.05 mg, 0.002 mmol) in 3:1 *tert*-amyl alcohol/DCM were stirred at −25 °C for 20 h to afford unreacted alcohol *S*-**20a** 48.7% ee, and nicotinate *R*-**21** 82.8% ee (after hydrolysis); $s = 17$ and $c = 37\%$. GLC analysis after hydrolysis: SUPELCO BETA-DEX 120, 110 °C, 1.9 mL/min carrier gas flow. Retention times 18.2 min (*R*), 22.2 (*S*). For **21** (R^1 = 2-MeC_6H_4, R^2 = Me): HRMS calcd for $C_{15}H_{15}NNaO_2$ [M + Na]; ESMS m/z = 264.0995, found 264.0992; IR (neat, cm^{-1}) 1717, C=O; 1590, C=N; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.29 (1H, d, J = 1.5 Hz) 8.78 (1H, dd, J = 4.9, 1.5 Hz) 8.32 (1H, dt, J = 7.8, 2.0 Hz) 7.50 (1H, dd, J = 7.3, 1.5 Hz) 7.38 (1H, dd, J = 7.8, 4.9 Hz) 7.38−7.14 (3H, m) 6.35 (1H, q, J = 6.8 Hz) 2.45 (3H, s) 1.67 (3H, d, J = 6.8 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ 164.4, 153.3, 150.9, 139.6, 136.9, 134.7, 130.5, 127.8, 126.9, 126.3, 125.2, 123.2, 70.6, 21.5, 19.2.

Table 2, Entry 5: Isobutyroylation of 20a with 18b. Following the general procedure A, racemic **20a** (13.6 mg, 0.1 mmol), isobutyric anhydride (42 μL, 0.25 mmol), and catalyst **18b** (0.9 mg, 0.002 mmol, 95% ee) in 3:1 *tert*-amyl alcohol/DCM were stirred at −25 °C for 64 h to afford unreacted alcohol *R*-**20a** 69.9% ee and isobutyrate *S*-**22a** 69.0% ee (after hydrolysis); $s = 14$[26] and $c = 50.2\%$.

Table 2, Entry 6: Nicotinoylation of 20b with 8d. Following the general procedure B, racemic **20b** (17 mg, 0.1 mmol), nicotinic anhydride (14 mg, 0.06 mmol), and catalyst **8d** (0.05 mg, 0.002 mmol added as a solution of the free phosphine) in 3:1 *tert*-amyl alcohol/DCM were stirred at rt for 20 h to afford unreacted alcohol *S*-**20b** 48.8% ee and nicotinate *R*-**21** 94.4% ee (after hydrolysis); $s = 57$ and $c = 34\%$. HPLC analysis after hydrolysis: CHIRALCEL OD analytical column, 3% 2-propanol/hexanes, 1 mL/min flow rate. Retention times 11.8 min (*S*) (minor) according to (−) sign of optical rotation[27] 18.4 min (*R*) (major). For **21** (R^1 = C_6H_5, R^2 = *t*-Bu); HRMS calcd for $C_{17}H_{20}NO_2$ [M + H]; ESMS m/z = 270.1489, found m/z = 270.1479; IR (neat, cm^{-1}) 1723, C=O; 1590, C=N; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 9.33 (1H, d, J = 2.4 Hz) 8.79 (1H, dd, J = 4.8, 1.8 Hz) 8.33 (1H, dt, J = 7.8, 1.8 Hz) 7.44−7.23 (6H, m) 5.75 (1H, s) 1.04 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$, ppm) δ 164.3, 153.4, 150.8, 137.9, 132.1, 127.8, 127.6, 126.4, 123.3, 89.1, 68.8, 35.4, 26.1.

Table 2, Entry 7: Isobutyroylation of 20b with 18b. Following the general procedure A, racemic **20b** (16.4 mg, 0.1 mmol),

isobutyric anhydride (42 μL, 0.25 mmol), and catalyst **18b** (0.8 mg, 0.002 mmol, 95% ee) in 3:1 *tert*-amyl alcohol/DCM were stirred at −25 °C for 64 h to afford unreacted alcohol *R*-**20b** 50.9% ee and isobutyrate *S*-**22b** 66.8% ee (after hydrolysis); $s = 9.9$[26] and $c = 43\%$.

General Procedure for Parallel Kinetic Resolution Using Catalysts 8d and 18b. Under Ar, a solution of **5** (0.1 mmol), nicotinic anhydride (23 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol, degassed), and Et_3N (22 μL, 0.15 mmol) in 3:1 *tert*-amyl alcohol/CH_2Cl_2 (0.8 mL) was cooled to −25 °C in a Cryocool. Catalysts **8d** and **18b** (amounts based on the rate predicted from control experiments A and B assuming a linear relationship between the amount of catalyst and the rate) were taken up in 3:1 *tert*-amyl alcohol/CH_2Cl_2 (0.2 mL) and added to the reaction mixture. The reactions were stirred until the alcohol reactant was consumed (several days). The mixture was concentrated (aspirator), and the ratio of products was determined by crude NMR. The products were purified by flash chromatography. Ester fractions were concentrated to afford **21** and **17**. Next, 5% NaOH/MeOH (1 mL) was added to saponify each ester prior to assay. The solution was warmed gently for 5 min and then left at room temperature for 2 h. Methanol was evaporated, and the residue was filtered through an 8 × 1.2 cm pad of silica gel in CH_2Cl_2. After solvent removal (aspirator), HPLC assay for each product was carried out on a chiral support.

Table 3, Entry 2: PKR of 5. Following the general procedure, racemic **5** (17 mg, 0.1 mmol), **8d** (ca. 0.001 mmol), and **18b** (3.3 mg, 0.007 mmol, 95% ee) were stirred for 69 h to afford 14 mg (51%) of *R*-**21** 65.3% ee (after hydrolysis) and 11 mg (46%) of *S*-**17** 72.7% ee (after hydrolysis).

Table 3, Entry 4: PKR of 20a. Following the general procedure, racemic **20a** (14 μL, 0.1), **8d** (ca. 0.006 mmol), and **18b** (1.5 mg, 0.003 mmol, 95% ee) were stirred for 6 days to afford 12.6 mg (52%) of *R*-**21** 67.7% ee (after hydrolysis) and 9.1 mg (44%) of *S*-**22a** 82.3% ee (after hydrolysis).

Table 3, Entry 5: PKR of 20b. Following the general procedure, racemic **20b** (17.5 mg, 0.1 mmol), **8d** (ca. 0.006 mmol), and **18b** (2.2 mg, 0.005 mmol, 95% ee) were stirred for 6 days to afford 9.0 mg (33%) of *R*-**21** 79.3% ee (after hydrolysis) and 14.1 mg (60%) of *S*-**22b** 40.5% ee (after hydrolysis).

Table 4, Entry 1: Isobutyroylation of 5 with 23a. Following the general procedure A, racemic **5** (17 mg, 0.1 mmol), isobutyric anhydride (8 μL, 0.05 mmol), and catalyst **23a** (0.05 mL, 0.02 M in *tert*-amyl alcohol, 0.001 mmol) in *tert*-amyl alcohol were stirred at rt for 4 h to afford unreacted alcohol *S*-**5** 10.9% ee and isobutyrate *R*-**17** 41.8% ee (after hydrolysis); $s = 2.7$ and $c = 21\%$.

Table 4, Entry 4: Isobutyroylation of 5 with 23b. Following the general procedure A, racemic **5** (17 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol), and catalyst **23b** (0.4 mg, 0.001 mmol) in toluene were stirred at −40 °C for 4 h to afford unreacted alcohol *S*-**5** 47.5% ee and isobutyrate *R*-**17** 85.5% ee (after hydrolysis); $s = 20.5$ and $c = 36\%$.

Table 4, Entry 5: Isobutyroylation of 5 with 23b. Following the general procedure A, racemic **5** (17 mg, 0.1 mmol), isobutyric anhydride (8 μL, 0.05 mmol), and catalyst **23b** (0.05 mL, 0.02 M in toluene, 0.001 mmol) in toluene were stirred at −70 °C for 8 h to afford unreacted alcohol *S*-**5** 7.0% ee and isobutyrate *R*-**17** 92.9% ee (after hydrolysis); $s = 29$ and $c = 7\%$.

Table 4, Entry 6: Isobutyroylation of 20a with 23b. Following the general procedure A, racemic **20a** (17 mg, 0.1 mmol), isobutyric anhydride (21 μL, 0.1 mmol), and catalyst **23b** (0.05 mL, 0.02 M in toluene, 0.001 mmol) in toluene were stirred at −40 °C for 4 h to afford unreacted alcohol *S*-**20a** 36.2% ee and isobutyrate *R*-**22a** 74.0% ee (after hydrolysis); $s = 9.5$ and $c = 33\%$. HPLC analysis: CHIRALCEL OB analytical column, 3% 2-propanol/hexanes, 1 mL/min flow rate. Retention times 13.4 min (*S*), according to (−) sign of optical rotation, 21.4 min (*R*).[14a]

Table 4, Entry 7: Isobutyroylation of 20b with 23b. Following the general procedure A, racemic **20b** (17 mg, 0.1 mmol), isobutyric anhydride (21 μL, 0.1 mmol), and catalyst **23b** (0.05 mL, 0.02 M in toluene, 0.001 mmol) in toluene were stirred at −40 °C for 4 h to afford unreacted alcohol *S*-**20b** 10.1% ee and isobutyrate *R*-**22b** 25.2% ee (after hydrolysis); $s = 1.8$ and $c = 29\%$. HPLC analysis: CHIRALCEL OD analytical column, 3% 2-propanol/hexanes, 1 mL/min flow rate. Retention times 11.8 min (*S*) according to (−) sign of optical rotation, 18.4 min (*R*).[14a]

***m*-Chlorobenzoylation of 5 with Phosphine 8d.** Following the general procedure B, racemic **5** (22 mg, 0.12 mmol), *m*-chlorobenzoic anhydride (29 mg, 0.1 mmol), and phosphonium salt **8d**·HBF_4 (0.05 mL, 0.04 M in toluene, 0.002 mmol) in toluene were stirred at −40 °C for 6 h to afford unreacted alcohol *S*-**5** 97.5% ee and isobutyrate *R*-**24** 65.3% ee (after hydrolysis); $s = 19.8$ and $c = 60\%$.

Representative Anhydride Competition Experiment. A solution of 1-naphthylmethylcarbinol **5** (17 mg, 0.1 mmol), *m*-chlorobenzoic anhydride (30 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol, degassed), and the phosphonium salt **8c**·HBF_4 (1.5 mg, 0.004 mmol) in toluene (0.7 mL) was treated with Et_3N (21 μL, 0.15 mmol). After the solution was stirred for 5 h, addition of *i*-$PrNH_2$ (0.1 mL) quenched the reaction, and the solvent was evaporated (N_2 stream). NMR assay of the reaction mixture revealed 18:1 of the *m*-chlorobenzoate to isobutyrate esters based on comparison of the spectrum with the spectra of the individual esters.

General Procedure for Parallel Kinetic Resolution Using Catalysts 8d and *ent*-23b. A solution of **5** (0.1 mmol), *m*-chlorobenzoic anhydride (23 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol, degassed), and Et_3N (22 μL, 0.15 mmol) in toluene (0.8 mL) was cooled to −40 °C in a Cryocool. The catalysts were added as solutions: phosphonium salt **8d**·HBF_4 (25 μL, 0.0022 mmol, 0.088 M in DCM) and *ent*-**23b** (25 μL, 0.001 mmol, 0.04 M in DCM). The reactions were stirred for 2−3 h and then quenched with *i*-$PrNH_2$ (0.1 mL). The mixture was concentrated (aspirator), and the ratio of products was determined by ^1H NMR spectroscopy. The products were purified by flash chromatography (2:1 Hex/Et_2O). Analytical TLC (2:1 Hex/Et_2O): *m*-chlorobenzoate, $R_f = 0.44$; isobutyrate, $R_f = 0.32$; alcohol, $R_f = 0.12$. Ester fractions were concentrated to afford **17** and **24**. Next, 5% NaOH/MeOH (1 mL) was added to saponify each ester prior to assay. The solution was warmed gently for 5 min and then left at room temperature for 2 h. Methanol was evaporated, and the residue was filtered through an 8 × 1.2 cm pad of silica gel in DCM. After solvent removal (aspirator), HPLC assay for each product was carried out on a chiral support as previously described.

Parallel Kinetic Resolutions. Table 5, Entry 1. Following the general procedure, racemic **5** (17 mg, 0.1 mmol), phosphonium salt **8d**·HBF_4 (0.0022 mmol), and *ent*-**23b** (0.001 mmol) were stirred for 3 h to afford *R*-**24**, 88% ee (after hydrolysis), *S*-**17**, 75% ee (after hydrolysis), and recovered alcohol **5**, 27% ee.

Table 5, Entry 2. Following the general procedure, racemic **5** (17 mg, 0.1 mmol), phosphonium salt **8d**·HBF_4 (0.0026 mmol), and *ent*-**23b** (0.001 mmol) were stirred for 3 h to afford *R*-**24** (14 mg, 44%) 87% ee (after hydrolysis), *S*-**17** (8 mg, 33%) 76% ee (after hydrolysis), and recovered alcohol **5**, 8% ee.

Table 5, Entry 3. Following the general procedure, racemic **5** (17 mg, 0.1 mmol), phosphonium salt **8d**·HBF_4 (0.0052 mmol), and *ent*-**23b** (0.002 mmol) were stirred for 2 h to afford *R*-**24**, 86% ee (after hydrolysis), *S*-**17**, 75% ee (after hydrolysis), and recovered alcohol **5**, 19% ee.

Preparation of Mixed Biphenyl Cyclohexyl Anhydride 29. A solution of 4-biphenyl carboxylic acid (999 mg, 5.0 mmol) in

THF (15 mL) was cooled to 0 °C, and NaH (204 mg, 5.1 mmol) was added. After 30 min, the solution was allowed to warm to rt and stirred for an additional 1 h. The solution was recooled to 0 °C, and cyclohexyl carbonyl chloride (0.61 mL, 4.5 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C. The ice bath was removed, and the mixture was stirred for an additional 40 min at rt. Activated carbon (~0.5 g) and hexanes (10 mL) were added, and the mixture was filtered through Celite and concentrated to yield a white solid. The solid was taken up in hot hexanes, filtered (to remove the symmetrical biphenyl anhydride), and allowed to cool to cool. Slow evaporation of the hexanes afforded **29** as a white crystalline solid and was used as soon as possible without further manipulation (478 mg, 35%): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.10 (2H, d, J = 8.2 Hz) 7.69 (2H, d, J = 8.2 Hz) 7.62 (2H, d, J = 6.9 Hz) 7.50−7.39 (3H, m) 2.61 (1H, tt, J = 10.9, 3.5 Hz) 2.14−2.06 (2H, m) 1.88−1.80 (2H, m) 1.72−1.56 (3H, m) 1.42−1.23 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 171.5, 147.0, 139.6, 130.9, 129.0, 128.5, 127.6, 127.4, 127.3, 44.2, 28.5, 25.6, 25.2.

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Supporting Information Available: ^{1}H and ^{13}C spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.