Nonenzymatic Dynamic Kinetic Resolution of Secondary Alcohols via Enantioselective Acylation: Synthetic and Mechanistic Studies

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Ⓢ *Supporting Information*

ABSTRACT: Because of the ubiquity of the secondary carbinol subunit, the development of new methods for its enantioselective synthesis remains an important ongoing challenge. In this report, we describe the first nonenzymatic method for the dynamic kinetic resolution (DKR) of secondary alcohols (specifically, aryl alkyl carbinols) through enantioselective acylation, and we substantially expand the scope of this approach, vis-à-vis enzymatic reactions. Simply combining an effective process for the kinetic resolution of alcohols with an active catalyst for the racemization of alcohols did not lead to DKR, due to the incompatibility of the ruthenium-based racemization catalyst with the acylating agent (Ac_2O) used in the kinetic resolution. A mechanistic investigation revealed that the ruthenium catalyst is deactivated through the formation of a stable ruthenium–acetate complex; this deleterious pathway was circumvented through the appropriate choice of acylating agent (an acyl carbonate). Mechanistic studies of this new process point to reversible N-acylation of the nucleophilic catalyst, acyl transfer from the catalyst to the alcohol as the rate-determining step, and carbonate anion serving as the Brønsted base in that acyl-transfer step.
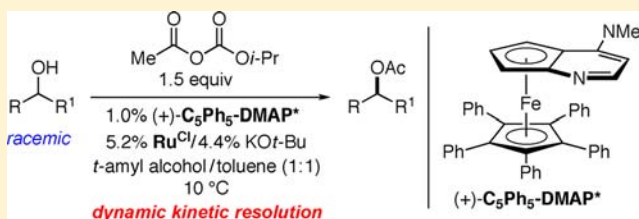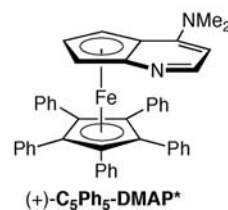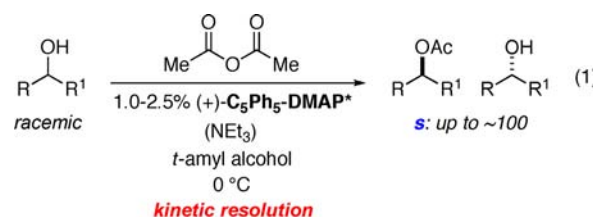
INTRODUCTION

Dynamic kinetic resolution (DKR) is a powerful strategy in asymmetric synthesis, allowing the stereoconvergent transformation of both enantiomers of a racemic substrate into a single enantiomer of a target molecule.[1] This approach overcomes a limitation of simple kinetic resolutions, which provide a maximum direct yield of 50% for a particular enantiomer. For an efficient DKR, the reaction conditions for kinetic resolution and for racemization of the substrate must be compatible, and racemization must occur rapidly relative to conversion of the slow-reacting enantiomer to product.

Because secondary carbinols are a common subunit in bioactive compounds,[2] a great deal of effort has been dedicated to the development of efficient methods for their synthesis in enantioenriched form.[3] Enzymatic resolution, including DKR, of racemic alcohols is one of the more widely used approaches, especially in industry.[4] With respect to enantioselective acylation,[5] although impressive progress has been described for enzymatic DKR's,[6] as well as for nonenzymatic (and nondynamic) kinetic resolutions,[7] we are not aware of any reports of useful nonenzymatic DKR's.

In previous studies, we established that a planar-chiral DMAP derivative serves as an effective catalyst for the kinetic resolution of a variety of racemic aryl alkyl carbinols,[8] propargylic alcohols,[9] and allylic alcohols[10] via acylation with Ac_2O, providing selectivity factors as high as ~100 (eq 1). Our early attempts to develop a *dynamic* variant were stymied either by the incompatibility of the acylation and the racemization processes, or else by the need for elevated temperature in order

to achieve racemization, which led to a substantial erosion in enantioselectivity.

Recent discoveries of catalysts that rapidly racemize secondary alcohols at room temperature[11] provided fresh impetus for us to revisit the unsolved challenge of developing an effective method for the nonenzymatic DKR of alcohols via enantioselective acylation. In this report, we describe the achievement of this objective through the use of a planar-chiral DMAP derivative (acylation catalyst) in combination with a ruthenium complex (racemization catalyst) in the presence of

an acyl carbonate (eq 2), and we present mechanistic studies, some of which were critical to the successful development of this process.

$$\text{(2)}$$

dynamic kinetic resolution

$$\mathbf{Ru^{Cl}}$$
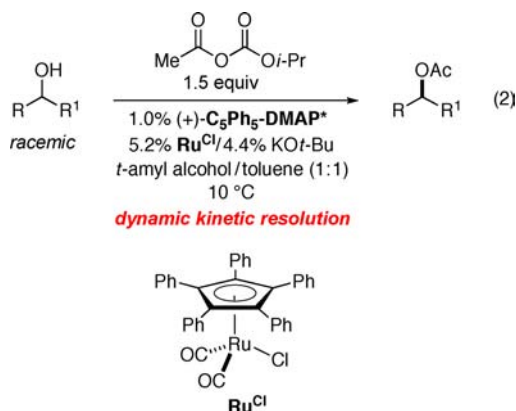
RESULTS AND DISCUSSION

A variety of transition-metal complexes have been reported to catalyze the racemization of secondary alcohols.[11] We were particularly drawn to the recent systematic studies of Bäckvall, who has established that $(C_5Ph_5)Ru(CO)_2(Ot\text{-}Bu)$ ($\mathbf{Ru^{Ot\text{-}Bu}}$), generated in situ from $(C_5Ph_5)Ru(CO)_2Cl$ ($\mathbf{Ru^{Cl}}$) and KOt-Bu, is an active racemization catalyst at room temperature, and that it can be applied to enzymatic DKR's of secondary alcohols.[12]
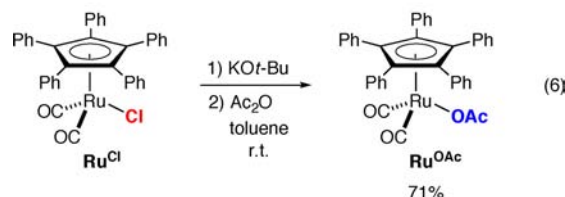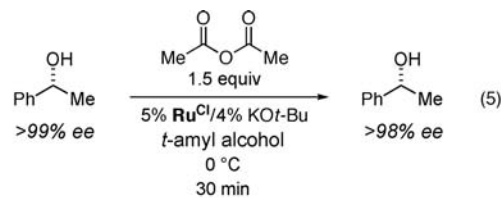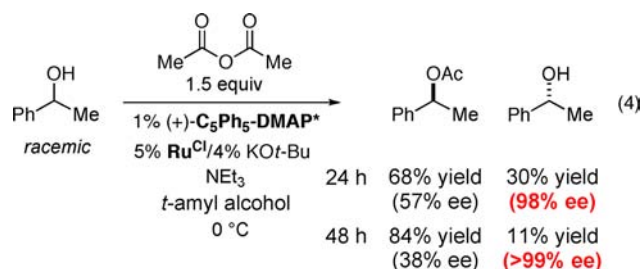
Bäckvall generally employs toluene as the solvent when utilizing $\mathbf{Ru^{Ot\text{-}Bu}}$ as a racemization catalyst, whereas t-amyl alcohol is the solvent of choice for kinetic resolutions catalyzed by $(\mathbf{C_5Ph_5})\textbf{-DMAP*}$ (eq 1). One could envision that use of an alcohol as the solvent might inhibit racemization of a secondary alcohol by $\mathbf{Ru^{Ot\text{-}Bu}}$; we have, however, determined that racemization of 1-phenylethanol proceeds smoothly in t-amyl alcohol even at 0 °C (eq 3. We employ a small excess of $\mathbf{Ru^{Cl}}$ in

$$\text{(3)}$$
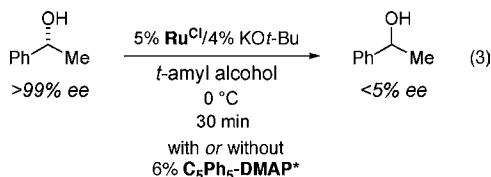
order to decrease the likelihood that adventitious KOt-Bu will have a deleterious impact on our DKR's, for example, by facilitating a Brønsted base-mediated nonenantioselective acylation). Furthermore, planar-chiral DMAP derivative $(\mathbf{C_5Ph_5})\textbf{-DMAP*}$ is compatible with the racemization process (eq 3), and no interaction between $\mathbf{Ru^{Ot\text{-}Bu}}$ (or the ruthenium alkoxide derived from 1-phenylethanol) and $(\mathbf{C_5Ph_5})\textbf{-DMAP*}$ can be detected in the ^{1}H NMR spectrum of a mixture of the two compounds in t-amyl alcohol/toluene.

Unfortunately, when we applied the conditions that we had developed earlier for the kinetic resolution of secondary alcohols (eq 1) to the DKR of 1-phenylethanol, it became clear that the ruthenium racemization catalyst is *not* compatible with the acylation process (eq 4). Thus, at partial conversion, the unreacted alcohol was substantially enantiomerically enriched (98% ee after 24 h; >99% ee after 48 h).

An additional control experiment revealed that $\mathbf{Ru^{Ot\text{-}Bu}}$ is deactivated by Ac$_2$O (eq 5 vs eq 3). We hypothesized that the ruthenium alkoxide might be acylated by Ac$_2$O to generate t-
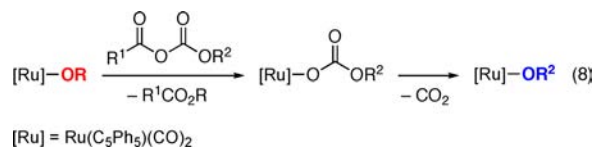
$$\text{(4)}$$

24 h	68% yield (57% ee)	30% yield (98% ee)
48 h	84% yield (38% ee)	11% yield (>99% ee)

$$\text{(5)}$$

$$\text{(6)}$$

$$\mathbf{Ru^{Cl}} \qquad \qquad \mathbf{Ru^{OAc}}$$
71%

butyl acetate and a ruthenium–acetate complex ($\mathbf{Ru^{OAc}}$), and indeed that has proved to be the case (eq 6). $\mathbf{Ru^{OAc}}$ is sufficiently stable that it can be purified by column chromatography and characterized by X-ray crystallography, which reveals an η^1-acetate ligand as part of an 18-electron ruthenium complex.

As we had conjectured, $\mathbf{Ru^{OAc}}$ is not an active racemization catalyst for 1-phenylethanol in t-amyl alcohol at 0 °C (eq 7; cf. eq 3). Furthermore, we have confirmed that $\mathbf{Ru^{OAc}}$ forms rapidly under the conditions that we had originally explored for the DKR of 1-phenylethanol (eq 4).[13]

$$\text{(7)}$$
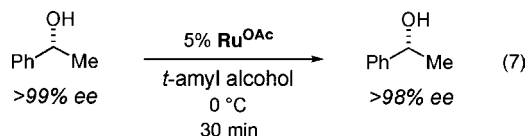
Thus, we needed to identify an acylating agent that would not deactivate the ruthenium–alkoxide racemization catalyst through the formation of a stable ruthenium carboxylate. Acyl carbonates[14] were among the array of candidates, since they are less electrophilic than anhydrides and, if acylation of the ruthenium alkoxide were to occur, the resulting ruthenium carbonate might decarboxylate and thereby regenerate a ruthenium alkoxide (eq 8).[15,16]

$$[Ru]\!-\!OR \xrightarrow[-R^1CO_2R]{} [Ru]\!-\!O\overset{O}{\underset{}{\|}}OR^2 \xrightarrow[-CO_2]{} [Ru]\!-\!OR^2 \quad (8)$$

$$[Ru] = Ru(C_5Ph_5)(CO)_2$$

Indeed, we have determined that, with acetyl isopropyl carbonate[17] as the acylating agent in a mixture of the preferred solvents for $(\mathbf{C_5Ph_5})\textbf{-DMAP*}$-catalyzed acylation (t-amyl alcohol) and $\mathbf{Ru^{Ot\text{-}Bu}}$-catalyzed racemization (toluene), the DKR of 1-phenylethanol proceeds with good ee and in

excellent yield (eq 9). We observe lower enantioselectivity and yield when other acyl carbonates are employed as the acylating agent.

(9)

R	R¹	ee (%)	yield (%)
Me	i-Pr	87	95
Et	i-Pr	76	78
Me	Et	78	67
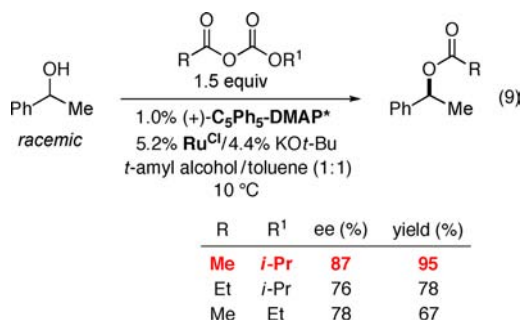
This method achieves the DKR of an array of aryl alkyl carbinols with ∼90% ee and in high yield (Table 1, entries 1−

Table 1. Nonenzymatic Dynamic Kinetic Resolution of Secondary Alcohols (for the Reaction Conditions, See eq 2)[a]

| entry	alcohol		ee (%)	yield (%)[b]
1		R = Me	87	95 (85)
2		Et	90	96 (95)
3		cyclopentyl	82	90 (86)
4		i-Pr	91	98 (95)
5		X = Cl	85	89 (88)
6		OMe	88	93 (92)
7			91	97 (96)
8			93	97 (92)
9			90	99 (94)
10			88	97 (90)

[a] All data are the average of two experiments. The predominant product is the S enantiomer. [b] The yield was determined by GC analysis with the aid of a calibrated internal standard. The yield of purified product is provided in parentheses.

9).[18] The scope of the process is relatively broad: for example, the alkyl substituent of the carbinol can range in size from Me to isopropyl. In contrast, *corresponding enzymatic DKR's of aryl alkyl carbinols are only effective when the alkyl group is not branched (in the α, β, or even the γ position).*[6]

Effective DKR is observed when the aromatic ring of the aryl alkyl carbinol is electron-poor or electron-rich (Table 1, entries 5 and 6), para-, meta-, or ortho-substituted (entries 5−8), or an extended π system (entry 9). Furthermore, the nonenzymatic DKR of an *allylic* alcohol can be achieved with useful enantioselectivity and yield (entry 10).

This combination of planar-chiral DMAP derivative (C₅Ph₅)-DMAP* and a ruthenium racemization catalyst can also be applied to the stereoconvergent acylation of a diol. Thus, when

three isomers of a diol are subjected to our DKR conditions, the C_2-symmetric bis(acetate) can be isolated in excellent ee (eq 10).

(10)

80% yield, 99% ee
(+11% meso)
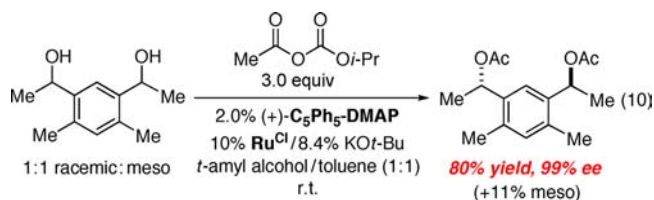
The rate law for the DKR of 1-phenylethanol is first order in 1-phenylethanol, first order in the acylation catalyst ((C₅Ph₅)-DMAP*), "fractional" (first order at low concentration, approaching zeroth order at higher concentration) order in acetyl isopropyl carbonate, and zeroth order in the racemization catalyst. According to an NMR spectroscopic study, the resting state of the planar-chiral DMAP derivative during a DKR is a mixture of the free catalyst and the N-acylated catalyst,[19] which accounts for the "fractional" dependence of rate on the concentration of acetyl isopropyl carbonate. Acyl transfer from the catalyst to the alcohol is likely the rate-determining step of the DKR (Figure 1).
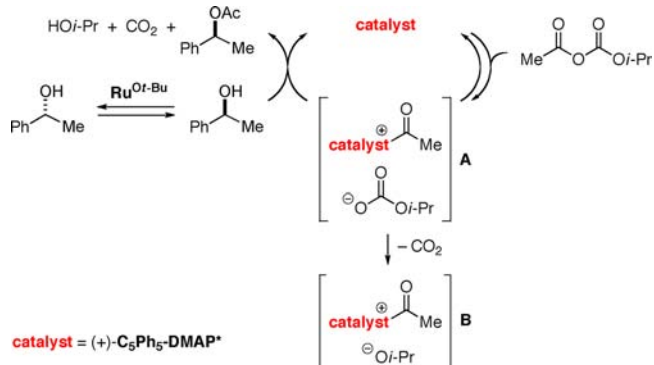

Figure 1. Outline of a mechanism for the nonenzymatic dynamic kinetic resolution of a secondary alcohol catalyzed by (+)-(C₅Ph₅)-DMAP* and Ru^Ot-Bu.

When (C₅Ph₅)-DMAP* is treated with 2 equiv of acetyl isopropyl carbonate at −20 °C, the acylpyridinium salt is generated almost quantitatively, according to ¹H NMR spectroscopy (eq 11).[20] The salt is stable for at least 6 h at this temperature.

(11)
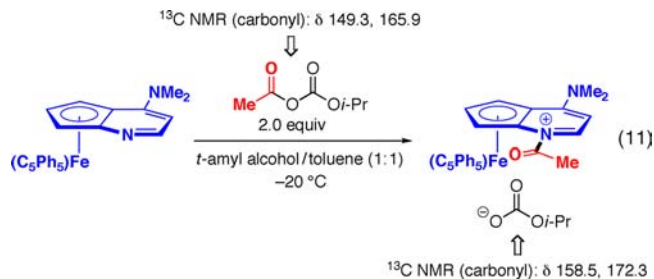
We hypothesize that ion pair **A**, rather than **B**, is the species that reacts with the secondary alcohol in the rate-determining acyl-transfer step of the reaction (Figure 1). Consistent with this suggestion, the decarboxylation of acetyl isopropyl carbonate in the presence of (C₅Ph₅)-DMAP* proceeds

significantly more slowly (eq 12; 5% after 3 h) than the acylation of 1-phenylethanol under DKR conditions (37% conversion after 3 h).
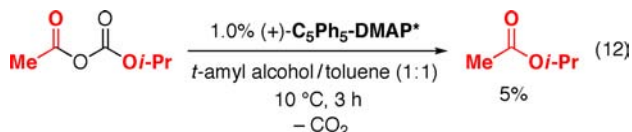
CONCLUSIONS

Dynamic kinetic resolution is a powerful approach to the enantioselective synthesis of secondary alcohols, an important family of bioactive compounds. We have developed the first nonenzymatic method for the DKR of alcohols through enantioselective acylation, and we have established that this process is effective for a variety of aryl alkyl carbinols (including a diol); this study complements corresponding enzymatic DKR's, which are not useful when the alkyl substituent is branched. We were not able to address this challenge simply by combining an effective method for the kinetic resolution of alcohols with an active catalyst for the racemization of alcohols—the two processes proved to be incompatible, specifically, the ruthenium-based racemization catalyst was poisoned by the acylating agent (Ac_2O) employed in the kinetic resolution. Nevertheless, we determined the pathway for deactivation (formation of a stable, inactive ruthenium–acetate adduct) and developed a method that circumvents this problem. Mechanistic studies (reactivity, kinetics, and spectroscopic) of this new process for the DKR of aryl alkyl carbinols indicate that N-acylation of the nucleophilic catalyst is reversible, acyl transfer from the catalyst to the alcohol is the rate-determining step, and a carbonate anion serves as the Brønsted base in that acyl-transfer step. The development of additional applications of planar-chiral DMAP derivatives in asymmetric catalysis is underway.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

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(12) Martín-Matute, B.; Edin, M; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825.

(13) Notes: (a) **Ru**$^{Ot-Bu}$ reacts with AcOH within 10 min at room temperature (in *t*-amyl alcohol/toluene (1:1)) to generate **Ru**^{OAc} and *t*-BuOH. (b) In the presence of propionic acid and 1-phenylethanol, **Ru**^{OAc} does not react to form a ruthenium-propionate adduct after 20 h at room temperature (in *t*-amyl alcohol/toluene (1:1)).

(14) For an example of the use of an acyl carbonate in an enzymatic kinetic resolution of an alcohol, see: Guibe-Jampel, E.; Chalecki, Z.; Bassir, M.; Gelo-Pujic, M. *Tetrahedron* **1996**, *52*, 4397–4402.

(15) We subsequently determined that **Ru**$^{Ot-Bu}$ does not react with acetyl isopropyl carbonate after 20 h at room temperature, in the absence or in the presence of 1-phenylethanol (in *t*-amyl alcohol/toluene (1:1)).

(16) Kim has reported that DMAP catalyzes the decarboxylation of acyl carbonates to form esters: Kim, S.; Lee, J. I.; Kim, Y. C. *J. Org. Chem.* **1985**, *50*, 560–565.

(17) Notes: (a) Acetyl isopropyl carbonate can be synthesized in one step from acetic acid and isopropyl chloroformate. After five days at room temperature under nitrogen, there is no detectable decomposition. (b) We are not aware of previous reports of the use of this acyl carbonate as an acylating agent for alcohols. (c) Whereas acylations of alcohols by Ac_2O generally include a stoichiometric Brønsted base as an additive (to capture AcOH), when acetyl isopropyl carbonate is used as the acylating agent, isopropyl alcohol is produced, and no added base is required.

(18) Notes: (a) On a gram scale, the DKR illustrated in entry 8 of Table 1 proceeded in 92% ee and >99% yield (1.25 g of product; catalyst recovery for **C₅Ph₅-DMAP***: 74%). (b) During the course of the DKR of 1-phenylethanol (Table 1, entry 1), the ee of the product was constant, and the ee of the unreacted starting material was less than 15%. (c) Under the conditions described in eq 2, a simple kinetic resolution (i.e., without **Ru^Cl** and KO*t*-Bu) of 1-phenylethanol proceeded with a selectivity factor of 14, a value consistent with the 87% ee that we observe for the DKR of 1-phenylethanol (Table 1, entry 1). (d) Under our standard conditions, DKR's of phenyl *t*-butyl carbinol and of phenyl chloromethyl carbinol were not effective. (e) Both enantiomers of **C₅Ph₅-DMAP*** are available from Strem Chemicals.

(19) Notes: (a) For spectroscopic characterization and X-ray structural analysis of N-acetylated **C₅Ph₅-DMAP***, see ref 9. (b) This DKR was conducted with 3.6% **(C₅Ph₅)-DMAP***, in order to facilitate analysis by ¹H NMR spectroscopy.

(20) For the reaction of acetyl isopropyl carbonate with **(C₅Ph₅)-DMAP***, lower temperature favors N-acylation.