Base-Free Dynamic Kinetic Resolution of Secondary Alcohols Using "Piano-Stool" Complexes of N-Heterocyclic Carbenes

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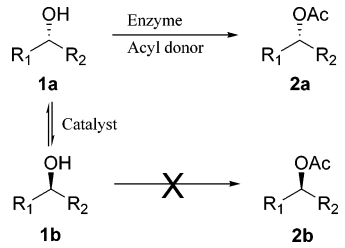
Summary: "Piano-stool" complexes of rhodium and iridium activated by fluorinated and non-fluorinated N-heterocyclic carbene (NHC) ligands were shown to be catalysts for racemization in the one-pot chemoenzymic dynamic kinetic resolution (DKR) of secondary alcohols. Excellent conversions and good enantioselectivities were observed for alkyl aryl and dialkyl secondary alcohols.

The production of enantiopure intermediates for the pharmaceuticals, agrochemical, materials, and flavor industries is still a major challenge to chemists. New emphasis on waste minimization and associated green chemistry has led to criticism of conventional kinetic resolution (KR) methods. In KR a biocatalyst selectively transforms one enantiomer in a racemic mixture and facilitates separation, but the maximum yield is only 50%. A protocol for combining the activity of chemical catalysts and biocatalysts in order to utilize 100% of the racemic mixture was reported by Williams and co-workers[1] for group 9 metals and Bäckvall and co-workers for Ru catalysts.[2] The technique, a form of dynamic kinetic resolution (DKR), operates as depicted in Scheme 1. A transition-metal-centered racemization catalyst interconverts the enantiomers by hydrogen transfer, allowing the enzymatic acylation of all the alcohol. Several excellent review articles on the subject have been published.[3]

The addition of an external base is an important variable. As reflected in the patent literature,[4] the majority of racemization catalysts require base to attain appreciable reaction rates. Unfortunately, bases can cause unwanted side reactions and loss of enantioselectivity and are incompatible with some delicate enzymes. Further efforts to reduce waste and remove "unwanted" reagents drive the need to develop processes that operate without external base.[5] Reports of base-free DKR by this protocol are rare, but Bäckvall has reported that Shvo's catalyst, $[Ru_2(CO)_4(\mu\text{-}H)(C_4Ph_4COHOCC_4Ph_4)]$,[6] catalyzes racemization in the DKR of secondary alcohols.[7] The presence of internal basic oxygen centers allow the catalyst to operate without external base at elevated temperatures, but reactions are relatively slow, and in some cases an additional hydrogen donor is required to prevent ketone formation. Although base was not required, addition of base increased the rate of reaction.

Scheme 1. Dynamic Kinetic Resolution of Secondary Alcohols



As part of our work on the catalysis of transfer hydrogenation by group 9 piano-stool complexes,[8] we have discovered a new class of carbene-promoted racemization catalyst for DKR that does not require base.

A role for NHC ligands in various hydrogen transfer reactions has been developing. For example, ruthenium complexes have been used in the transfer hydrogenation of ketones[9,10] and imines[10] and iridium complexes in Oppenauer-type oxidation[11] and transfer hydrogenation.[12] To our knowledge, NHC ligands have not been used in the DKR of secondary alcohols. We endeavored to exploit the ability of carbene complexes to catalyze hydrogen transfer reactions without external base[9−11] to create new base-free chemoenzymic DKR processes.

In this study we have employed piano-stool complexes with NHC ligands as catalysts for racemization in the DKR of secondary alcohols in the presence and absence of an external base and studied the effect of fluorination of the substituents of the carbene ligand.

Rhodium and iridium complexes with an NHC ligand containing polyfluoroaryl groups, **3** and **4**,[13] and a nonfluorinated analogue, **5**[14] (Figure 1), have been reported previ-

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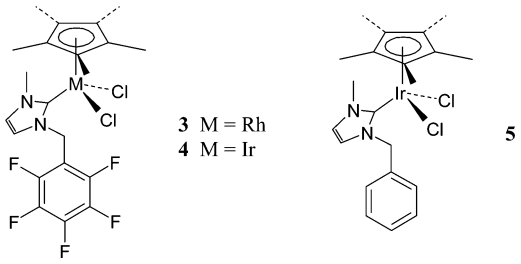
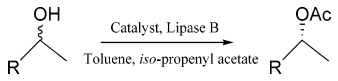


Figure 1. Racemization catalysts with NHCs.

Scheme 2. Dynamic Kinetic Resolution of Racemic Secondary Alcohols



ously. The intramolecular C−H activation activity of **5** was recently reported,[14] and although no similar activity was observed in our hands, this potential side reaction suggests a role for fluorination in suppressing unwanted reactivity.

DKR was performed on racemic secondary alcohols using *Candida antarctica* lipase B catalyzed esterification with isopropenyl acetate as the acyl donor at 70 °C (the safe upper temperature of the enzyme),[15] varying the racemization catalyst (Scheme 2 and Table 1). The use of isopropenyl acetate as the acyl donor gives the side product acetone, which is easily removed from the reaction mixture.[3] Initial comparison was conducted using *rac*-phenylethanol as the substrate (entries 1−11), as this is standard practice for DKR.[3] The activities of **3**−**5** were compared with a more conventional amino alcohol promoted catalyst,[4] [Cp*RhCl(μ-Cl)]$_2$, promoted by *S*-phenylglycinol. The results reveal a marked dependence on base for the *S*-phenylglycinol-promoted catalyst (catalyst **6**, entries 4 and 11); the 50% conversion observed in the absence of base is equivalent to lipase activity in the absence of any racemization activity. No such dependence was observed for NHC-bound catalysts **3**−**5**; NHC complexes consistently yielded high conversions in the absence and presence of base, with reasonable enantioselectivity (>95% enantiomeric excess (ee)).

To investigate the scope of this new catalyst system, **3**−**5** were applied to the DKR of two further alcohols, *rac*-3,3-dimethyl-2-butanol (entries 12−17) and *rac*-1-cyclohexylethanol (entries 18−20).

In the DKR of the sterically demanding alkyl alcohol *rac*-3,3-dimethyl-2-butanol, complexes **3** and **4** gave low enantioselectivity (55 and 70% respectively) in the absence of base, whereas the unfluorinated complex **5** yielded higher conversions (89%) and excellent enantioselectivity (ee 99%). The fluorine defers larger steric bulk to catalysts **3** and **4**, and this may be detrimental to racemization for bulky substrates, as it will increase the rate of substrate dissociation. In order to go through a racemization cycle the alcohol must bind, convert to a planar state by hydride abstraction, and flip over before receiving hydride on the opposite face; large steric clashes will cause premature dissociation, reducing alcohol racemization. A competing process of ester racemization is eroding the percent enantiomeric excess; this may be occurring by an outer-sphere mechanism, as is favored by the bulkier catalysts **3** and **4**.[3] Catalysts **3** and **5** were improved by the addition of base (compare entries 12 and 15 and entries 14 and 17); however, the Ir catalyst of the fluorinated NHC **4** lost enantioselectivity

Table 1. Results of DKR of Racemic Secondary Alcohols[a]

entry	R	cat.	yield (%)	ee (%)
1[b]	Ph	**3**	>99	97
2[b]	Ph	**4**	>99	95
3[b]	Ph	**5**	93	97
4[b]	Ph	**6**	50	96
5[c]	Ph	**3**	88	96
6[c]	Ph	**4**	95	97
7[c]	Ph	**5**	88	97
8[d]	Ph	**3**	95	97
9[d]	Ph	**4**	>99	95
10[d]	Ph	**5**	>99	97
11[d]	Ph	**6**	96	98
12[b]	$C(CH_3)_3$	**3**	65	55
13[b]	$C(CH_3)_3$	**4**	79	70
14[b]	$C(CH_3)_3$	**5**	89	99
15[d]	$C(CH_3)_3$	**3**	89	99
16[d]	$C(CH_3)_3$	**4**	97	58
17[d]	$C(CH_3)_3$	**5**	99	99
18[c]	C_6H_{11}	**3**	>99	99
19[c]	C_6H_{11}	**4**	>99	61
20[c]	C_6H_{11}	**5**	>99	99

[a] Conditions: 0.0072 mmol of catalyst, 7.19 mmol of isopropenyl acetate, 7.2 mmol of secondary alcohol, 40.5 mg of Novozyme 435, 2.4 mL of toluene, 70 °C. [b] 18 h. [c] 8 h. [d] 0.26 g of K_2CO_3 added, 18 h.

(entries 13 and 16). This highlights the unpredictable nature of this complex interdependent chemoenzymic system.

The alkyl alcohol *rac*-1-cyclohexylethanol (entries 18−20) was converted efficiently to a chiral ester in the absence of base. Complexes **3**−**5** all showed excellent activity after only 8 h (>99% conversion). However, only complexes **3** and **5** gave excellent enantioselectivity (ee >99%); **4** gave a considerably lower enantioselectivity (61%).

DKR of the dialkyl alcohols *rac*-3,3-dimethyl-2-butanol and *rac*-1-cyclohexylethanol was highly successful for **5** (entries 14, 17, and 20), moderately successful for **3** (entries 12, 15, and 18), and relatively unsuccessful for **4** (entries 13, 16, and 19). The larger steric bulk of *rac*-3,3-dimethyl-2-butanol makes it a more challenging substrate and counteracts the benefits of fluorination observed for *rac*-phenylethanol; for this substrate, base is required to maximize the catalytic performance. The poor activity and selectivity of **4** are difficult to rationalize and may be due to competing reactivity, perhaps an outer-sphere[3] ester racemization.

The postrun integrity of catalyst **3** was proven by recovering the catalyst after a catalytic run.

In conclusion, "piano-stool" complexes with simple N-heterocylic carbene ligands are successful racemization catalysts in base-free DKR of secondary alcohols. Aryl alkyl and dialkyl secondary alcohols can be converted efficiently using fluorinated and non-fluorinated carbene ligands as activators. Base-free conversion to the (*R*)-acetate was demonstrated for *rac*-phenylethanol using catalysts **3**−**5** and for *rac*-1-cyclohexylethanol using catalysts **3** and **5**, but the bulkier substrate *rac*-3,3-dimethyl-2-butanol was efficiently converted only by the non-fluorinated catalyst **5**.

The removal of reagents that are not incorporated into the product, such as acids and bases, is an important goal in green chemistry.[16] In these reactions the effect of removing base is clearly observed (Figure 2); the base-free reaction mixtures were optically transparent, and the supported enzyme was easily separated, in comparison to the dull suspensions generated by the presence of K_2CO_3. Base-free processes open opportunities for new one-pot chemoenzymic processes using more delicate enzymes that are intolerant to the presence of base.

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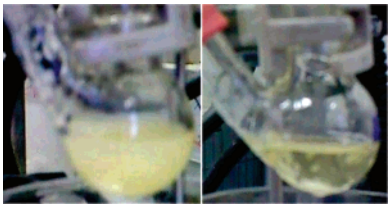

Figure 2. Base (left) and base-free (right) methods of DKR.

Experimental Section. (a) General Considerations. The compounds (*S*)-2-phenylglycinol, *rac*-1-cyclohexylethanol, *rac*-3,3-dimethyl-2-butanol, and isopropenyl acetate (Aldrich), *rac*-1-phenylethanol (Fluka), Novozyme 435 (*Candida antarctica* lipase B immobilized on acrylic resin) (Sigma), and potassium carbonate (Lancaster) were used as supplied. The complexes **3** and **4** were prepared as previously described;[13] complex **5**[14] was prepared analogously to **4**.[13] Catalytic studies were performed in anhydrous toluene (Aldrich) under dinitrogen.

^{1}H and ^{19}F NMR spectra were recorded at 25 °C using Bruker DPX300 and DRX500 spectrometers. ^{1}H spectra (300.01 or 500.13 MHz) were referenced internally using the residual protio solvent resonance relative to $SiMe_4$ (δ 0), and ^{19}F spectra were referenced (282.26 MHz) externally to $CFCl_3$ (δ 0). All chemical shifts are quoted in δ (ppm), using the high-frequency positive convention, and coupling constants in Hz. LSIMS was recorded on a VG Autospec X series mass spectrometer. Elemental analyses were carried out by the ASEP, The School of Chemistry and Chemical Engineering, Queen's University Belfast. HPLC was performed using an Agilent 1100 with a chiral AD-H column: wavelength, 190 nm,; column flow, 1 mL/min; solvent ratio, 95/5 (hexane/propan-2-ol); injection volume, 5 μL.

(b) Procedure for Dynamic Kinetic Resolution. A mixture of complex **3**, **4**, or **5** (0.0072 mmol) or (*S*)-2-phenylglycinol (0.99 mg, 0.0072 mmol) and $[Cp^*RhCl(\mu\text{-}Cl)]_2$[17] (**6**; 2.23 mg, 0.0036 mmol), isopropenyl acetate (0.720 g, 7.19 mmol), and racemic secondary alcohol (7.2 mmol) in toluene (2.4 mL) was stirred at 70 °C for 15 min under dinitrogen (for entries 8−11 and 15−17 in Table 1 potassium carbonate (0.26 g, 2.30 mmol) was added to the mixture). Novozyme 435 (40.5 mg) was added and the reaction mixture stirred at 70 °C under dinitrogen for 18 h (entries 1−4 and 8−17) or 8 h (entries 5−7 and 18−20). The mixture was then filtered through silica (ca. 6 cm) and eluted with 10/1 hexane/diethyl ether (3 × 5 mL). The solvent was removed from the filtrate by rotary evaporation to afford a colorless liquid. ^{1}H NMR spectroscopy was used to determine the conversion, and percent ee values were determined by HPLC.[18−20]

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